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## THE NEWER ANTIHISTAMINES\*

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THE development of the antihistamine drugs has been one of the most interesting of the recent advances in therapeutics. They do not save life but they do provide a great advance in the management of several distressing if not dangerous maladies. More important, they have provided an important aid in the study of anaphylaxis and allergy. Perhaps this is their greatest ultimate value. The allergic diseases helped by these drugs are, in a sense, trivial but a large number of people suffer from them and physicians must welcome an aid which is effective symptomatically.

Since Dale and Laidlaw first showed, in 1911, that the immediate symptoms of anaphylaxis in animals were, to a large extent, the same as those produced by histamine, it has become almost universally accepted that histamine, or H-substance, plays an important part in anaphylactic phenomena. While anaphylaxis and allergy are not identical there is much similarity and it has been shown that histamine or a related substance, plays an important rôle in producing some allergic manifestations. In recent years several substances have been found which will prevent the action of histamine on the isolated guinea pig intestine and in the intact animal. These substances also protect the animal from the effects of anaphylactic shock. It is not surprising then that some of these substances also relieve man from a variety of allergic manifestations.

In a recent communication<sup>1</sup> I presented a brief outline of the histamine theory of anaphylaxis and allergy and of the development of the so-called antihistamine drugs. It was pointed out that while it was highly probable

that histamine, or a closely related substance, was liberated by the antigen-antibody reaction and accounted for many of the observed manifestations of anaphylaxis and allergy, it did not account for them all. This supposition has been borne out by the fact that the various antihistamine drugs dramatically influence some allergic manifestations and fail to affect others.

Animal experiments have shown that these drugs are powerful histamine antagonists but all of the pharmacological properties of histamine are not affected. For example using pyribenzamine as an antagonist, animals have been protected from anaphylactic shock when many times the lethal dose of histamine was given, but the animals often succumbed later to peritonitis from a perforated peptic ulcer. Evidently the action of histamine on gastric secretion was not inhibited.

The pharmacological action in man would appear to be primarily antihistamine although the complex chemical structure of the drugs suggests many subsidiary properties. The many observed reactions, particularly on the nervous system, would indicate that possibly some of the clinical effects are other than those of antihistamine. However, present evidence indicates that prompt response to the drug indicates antagonism to histamine. Recently it was shown by Curry and Lowell that when histamine aerosol was inhaled by man bronchial asthma would result. This could be prevented or promptly relieved with pyribenzamine. When acetyl-beta-methyl choline was inhaled in an aerosol asthma was also produced but pyribenzamine was quite ineffective in preventing or relieving it. Clinically the antihistamine drugs have been notably ineffective in asthma and this suggests, of course, that histamine is not a mediator of asthma in most instances in man.

The many published clinical reports<sup>2</sup> indicate clearly that these drugs vary in degree but have quite similar actions. Clinically they have

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favourable effects on urticaria and on the itching of atopic dermatitis. Hay fever of all kinds seems to be benefited in a large proportion of cases. The effects in asthma have been very disappointing. The antihistamines have also been used with benefit in preventing or treating reactions to allergic hyposensitization. Their local application to the conjunctiva, the nose and the skin also has some promise. Unfortunately the toxic and side effects of the drugs have been prominent.

A number of chemically related compounds have been developed in an effort to produce more potent antihistamine effects and less toxicity. This has been done with some success and it may be expected that still further compounds will become available which might be more valuable clinically. In the past fifteen months four such compounds have appeared on the market in Canada and it has been my good fortune to have had a supply of each for clinical investigation. In a recent communication I reported our experience with benadryl. In this paper I will report a similar series treated with antistine, pyribenzamine and neo-antergan.

A glance at their structural formulæ will show their close chemical relationship.

#### ANTISTINE

Antistine was synthesized by K. Mieseher of the Ciba Laboratories in Switzerland and its pharmacological and clinical properties were reported in several papers<sup>3,4</sup> in April, 1946. Chemically it is N. phenyl-N. benzyl-amino-methyl-imidazoline.

Animal experiments show that it is only feebly toxic and has slight cumulative capacity. It is also non-irritant when applied locally. It is a powerful histamine antagonist as shown in experiments on the isolated guinea pig intestine and in the intact animal. It was also found to be highly effective in protecting the rabbit and guinea pig from the immediate effects of anaphylactic shock. Several clinical reports<sup>3,4</sup> in the Swiss literature indicate that the drug is quite comparable to the other known antihistamine substances and has a very low toxicity.

Antistine is readily soluble in water and being only slightly irritant and having a very low anæsthetic value it has been used locally in the eye and in the nose, usually in combination with privine. It was used intravenously and intramuscularly as well as by mouth.

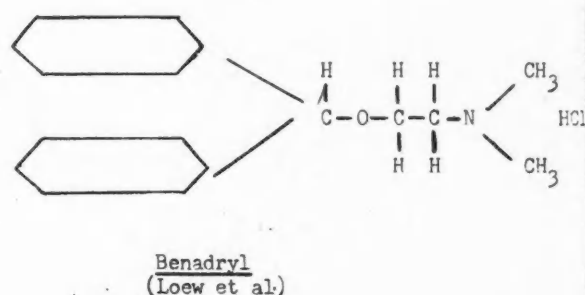
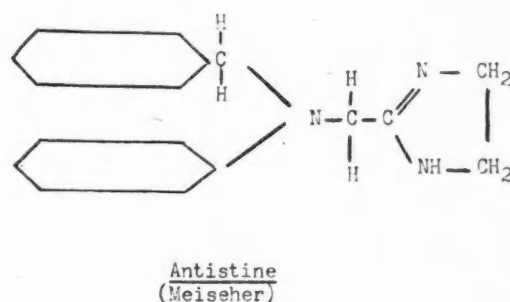
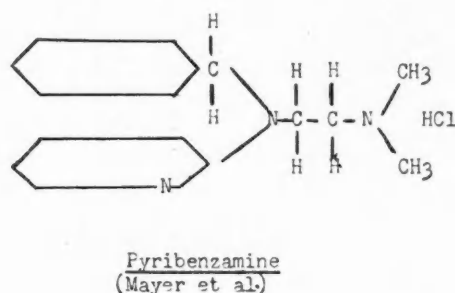
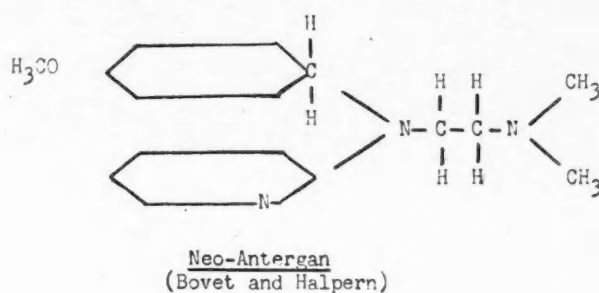


TABLE I.  
ANTISTINE

	No. cases	Improved	Not improved	Toxic effects
Allergic rhinitis:				
Perennial ....	44	32	12	14
Seasonal .....	4	4	0	1
Asthma .....	14	1*	13†	3†
Urticaria .....	10	8	2	1
Atopic dermatitis..	8	4	4	1
Migraine .....	3	2	1	1
	83	51	32	21

\* Prevented asthmatic reaction occurring with pollen hyposensitization.

† Two cases were greatly aggravated and necessitated prompt discontinuance.



TABLE II.  
ANTISTINE  
ALLERGIC RHINITIS—PERENNIAL

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
ER	56	F	100-300	Complete relief for 10-12 hours	Nil	No allergens demonstrated
MC	19	F	300	Complete relief	Nil	Pollen and danders, possibly foods. Associated with urticaria
VS	18	F	300	Fair relief	Felt faint and unsteady with each dose and could not continue drug after 2 days	Cause not finally established—food probable
WF	34	M	300	Excellent	Nil	Has assoc. asthma well controlled with hyposensitization. Pollen, mould, dust. A.R. symptoms developed Jan., 1947, for unknown reason and quickly controlled
RB	24	F	100 prn	Good	Nil	Cat sensitive
RHE	33	F	400	Fair	Nil	Pollen and animal dander and dusts. Associated asthma not affected
GS	17	F	100 prn	Quick complete relief	Nil	Feather and cosmetic sensitive. These factors now controlled
RS	15	F	400	Nil	Nil	Pollen, house dust, feathers and animal. Good effect with PBZ
LH	26	F	400	Nil	Slight feeling of fullness in face	PBZ gave +8 hours' relief. Feather and dust sensitive and probably an endocrine factor
ADM	56	M	400	Fair relief to sneezing and obstruction	Nil	Food and tobacco sensitive
ND	19	M	400 and 600	No effect	Nil	Animal, dust and cat sensitive
TGB	49	F	400	Moderate relief	Indigestion	Better relief with PBZ—cause not found
RW	25	M	400	Good relief for several hours	Nil	Cause not discovered
JM	34	F	400 and 600	Nil	Drowsy—blurred vision and felt very unwell but no g.i. upset	Very good PBZ effect
SJ	35	M	400	Nil	Nil	Marked cardiac anxiety and doubtful if rhinitis is allergic
MR	36	F	400 and 100 prn	Good	Nausea at first—none more recently	Associated asthma probably not benefited
BC	19mo.	M	50, O.H.8	Nil	Fine macular rash about neck	Cause not determined but dog and canary suspected
EE	25	F	400	Nil	Nil	Not tested likely premenstrual V.R.
OM	27	F	100 prn	Rapid relief lasting several hours	First dose made her light headed—nil with subsequent doses	Dust and feathers
GD	7	M	150	Nasal obstruction much improved and cough lessened	Nil	Dust, feather and cosmetic sensitive
FM	13	M	200	Moderate relief	Nil	Food and dust sensitive
RM	24	M	400 and 100 prn	Fairly good relief	Very drowsy	Grain and house dust
WB	26	M	100 prn	Nil	Nil	PBZ effective. Pollen, dust, feathers and orris root
MS	26	F	100 prn	Quick and full relief for several hours	Nil	Food sensitive, especially to pineapple
BS	47	F	300	Nil	Nil	Good relief with PBZ
JS	15	F	150	Fairly good relief for few hours	Sl. drowsy—later stopped because of drowsiness	Also subthyroid
MK	25	F	300 and 100 prn	Good	Nil	Pollen, animals and feathers. Relief with benadryl but too toxic.
KG	24	M	200	Good	Nil	Recurrent polypi and when these recurred had no antistine relief—Better result with PBZ but it made him sleepy
SCR	31	M	300 and 400	Fair	Nil	Associated asthma unaffected. Chicken sensitive (chicken farm!). Results of antistine gradually wore off with poorer effects

TABLE II.—Continued

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
JC	15	F	200 prn	Good temporary	Nil	Animal and feather sensitive
EHW	25	M	200 prn	Fairly good	Nil	Good benadryl relief previous but it led to paræsthesiæ of hands and was discontinued
AH	23	F	100 prn	Fairly good	Nil	No effect on asthma. PBZ similar
CS	39	F	400	Nil	Nil	Cause not found
DR	18	F	300	Good relief	Nil	No allergic investigation
WMM	30	F	400	Fairly good relief	Nil	Better relief with PBZ—is pregnant— not investigated
JK	18	M	400	Much improved	Nil	Dust, animal, pollen and mould— farmer
BB	27	F	400	Fair relief	Nausea, anorexia and slight dizziness with more than 300 daily	No relief to itching of atopic dermatitis
WW	46	M	400	Nil	Nil	V.R.—no cause demonstrated—associated headache attributed to milk?
AL	31	F	100 prn	Prompt and complete for several hours	Nil	Pollen and dust
DD	21	F	100 prn	Fair relief	Asthma aggravated	
VR	19	F	100 prn	Moderate relief	Nil	House and grain dust, animals, feathers and pollen
HYL	57	F	100 prn	Fair amount relief	Severe exacerbation of asthma	Severe exacerbation of asthma as with benadryl and neo-antergan
WJP	47	F	400	Nil	Nausea and vomiting	Discontinued drug and was unwell for succeeding four days
VO	17	F	100 prn	Relief within four hours	Irritable, restless and sleepy	Dust, feathers and pollen
OM	27	F	100 prn	Rapid complete relief for several hours	Nil	Dust, animals, feather sensitive

Given by the vein it was necessary to inject it slowly to prevent flushing and giddiness but otherwise presented no great difficulty in doses of 100 mgm.

I was happy to have the privilege of trying antistine therapeutically and am indebted to the Ciba Company Ltd., of Canada for a generous supply of the drug in December, 1946. In the past seven months I have observed its action on 83 patients and this preliminary report will indicate its effects relative to the other available antihistamine drugs. In all cases it has been administered by mouth. While I had ampoules of antistine suitable for parenteral administration I had no case in which such administration seemed to be necessary. In one

case in which the drug caused troublesome nausea and vomiting, the patient, understandably, would not consent to its use by any other route. However, I do think that its use parenterally will have a place in special cases.

Table I summarizes my experience in 83 allergic cases treated with antistine. Tables II to VII give more detail for the individual cases.

It is very difficult to report clinical results accurately when the observer must depend largely on subjective symptoms. Close cross examination is frequently necessary to obtain reliable data. It was not unusual for a patient to report benefit, enthusiastically, and, on close inquiry, to discover that the nasal symptoms were almost completely controlled but that the

TABLE III.  
ANTISTINE  
ALLERGIC RHINITIS—SEASONAL

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
JDF	47	F	100 prn	Good relief for 6 to 7 hours	Nil	Tree pollen—no effect on asthma
LMS	37	F	100 prn	Quick complete relief for several hours	Nil	Tree pollen, especially elm
EJR	36	F	400	Fairly good relief and in particular liked sedative effect!	Mildly drowsy—settled her nerves	Tree pollinosis
WD	30	F	100 prn	Good	Nil	No effect on asthma— tree sensitive

TABLE IV.  
ANTISTINE  
ASTHMA

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
MK	47	M	300	Questionable I.Q. low!	Nil	Fall exacerbation but symptoms throughout year—cause not definite.
WB	25	F	300	Nil	Nil	Relief with franol—no improvement with pregnancy
JOF	47	F	400 and 100 prn	Excellent relief to A.R. for several hours. No effect on asthma	Nil	See A.R. Table—seasonal
RHE	33	F	400	Nil though A.R. helped	Nil	See notes in perennial A.R. table
LM	52	F	400	Nil	Upset stomach	Infective asthma
HYL	56	F	300	Nil—in fact aggravated	Asthma worse as with benadryl and neo-antergan	Animal, feathers, cosmetics, dust, pollen
SCR	31	M	300	Nil	Nil	Some relief to rhinitis
AH	23	F	100 prn	Nil	Nil	Nasal relief only
AP	39	M	400	Nil	Nil	Thinks benefit from PBZ—poor observer
MR	36	F	400	Doubtful	Nausea at first	Associated rhinitis much relieved—probably food sensitive
CB	13	M	100 before hyposensitization	Marked aggravation to asthma in 15 minutes under observation	Aggravation	Tree pollinosis
EAL	37	M	100 before hyposensitization	Prevented reaction to pollen vaccination	Nil	Recent reactions to pollen therapy produce mild general reactions now prevented by antistine
WD	30	F	100 prn	Nil	Nil	Good relief to A.R.—trees
DD	21	F	100 prn	Aggravated	Aggravated	Fair relief to A.R.

TABLE V.  
ANTISTINE  
URTICARIA

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
MC	19	F	300	Complete and rapid relief	Nil	Acute urticaria as a result of strawberry sensitivity
MC	22 mo.	F	25 mgm. t.i.d. and later prn	Fairly prompt relief	Nil	Associated urticaria pigmentosa unaffected
SS	49	F	300	Marked and rapid relief	Nil	Etiology not discovered—large psychogenic element
FR	31	M	500	No relief	Nil	Ultimately proved to be reactive to raisins and easily controlled then
MS	26	F	100 prn	Complete	Nil	Also good relief to concurrent A.R. (food)
AW	40	F	300	Rapid	Nil	No effect with benadryl. Urticaria followed insulin used as shock therapy
JE	52	F	400	None	None	Liver sensitive (B.D.H.)
WPD	32	M	200 prn	Good relief	Nil	Also had a good and faster relief with benadryl but discontinued it because sensitivity suspected.
FZ	28	M	400	Fair relief to itching	Nil	Better relief with PBZ
VH	27	F	100 prn	Quick and good relief	300 mgm. within 3 hours caused weakness, dizziness and anorexia	Cause not found. But aspirin and chocolate strongly suspected. Rather unstable. Uses average of 200 mgm. daily to control hives as they appear



TABLE VI.  
ANTISTINE  
ATOPIC DERMATITIS

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
JE	52	F	300	Nil	Nil	Pernicious anæmia. Sensitive to B.D.H. liver
TO	35	F	300	Nil	Nil	Associated rhinitis. Relieved by avoiding yeast. Possibly slight improvement on PBZ
VH	28	M	400	Fair relief to itching for several hours	Nil	Sensitive to pollen, animals and orris root
ED	38	M	300 prn	No effect	Nil	Dermatitis developed while being hyposensitized for asthma which was well controlled. Later symptoms of A.R. were well controlled with PBZ
JDF	27	M	400 prn	Itching relieved	Nil	Ragweed dermatitis which persisted in winter, also ragweed hay fever
BS	30	M	400	Itching lessened	Nil	Pollen, dusts and food
BB	27	F	400 and 600	Nil—perhaps worse!	Nausea, anorexia and dizziness with doses over 300	Relieved associated rhinitis
GB	25	F	400	Doubtful	Nil	

TABLE VII.  
ANTISTINE  
MIGRAINE

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
JTM	36	F	400	No benefit	Drowsy	Severe associated psychoneurosis
EM	32	F	200 to 300 daily	Hemicrania greatly modified and interval extended from average of weekly to monthly—no further prostration or vomiting and felt "wonderful"	Nil	Probably food sensitive—fatigue chief precipitating factor
RE	25	F	Average 200	Remarkably free and headaches can often be prevented by prophyl. use—feels wonderful	Nil	Formerly good effect with benadryl but after several months had severe gastric upsets with vomiting and discontinued it

asthmatic symptoms had not improved, and that various asthmatic remedies such as ephedrine or epinephrine were being freely used. Similarly, toxic symptoms were difficult to evaluate. In general they were very mild, in contrast to benadryl, although in a few they were so severe as to require discontinuance of the drug. Although 21 cases or nearly 25% reported some degree of side effects less than 6% were severe. None has taken the substance long enough to evaluate possible long term toxicity.

In four cases of perennial rhinitis no relief was obtained with antistine using 400 mgm. daily, whereas 200 mgm. of pyribenzamine gave prompt and effective relief. In four others pyribenzamine gave greater relief. In one instance relief with the two drugs was about equal but pyribenzamine caused sleepiness

while there were no side effects with antistine. One case of urticaria also showed better symptomatic relief with pyribenzamine. Several cases in this group had favourable symptomatic relief previously with benadryl but had discontinued its use because of toxic effects which did not occur with antistine.

On the whole I think that the data given reflect a reasonably accurate picture of the

TABLE VIII.  
RESULTS OF PYRIBENZAMINE THERAPY

	No. of cases	Improved	Unimproved	Toxic
Allergic rhinitis:				
Perennial . . . . .	15	13	2	4
Asthma . . . . .	3	1	2	0
Urticaria . . . . .	3	2	1	1
Atopic dermatitis . . . . .	5	5	0	2
	26	21	5	7

TABLE IX.  
PYRIBENZAMINE  
PERENNIAL HAY FEVER

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
EM	28	M	200	Good relief for several hours	Nil	No effect on pruritus ani
JM	33	F	200	Doubtful benefit	Drowsy and left temporal pain	No antisthine effect. Trying neo-antergan
BS	47	F	100	Complete relief	Nil	No benefit with antisthine
WM	30	F	200	Almost complete relief	Slightly drowsy	Better relief than antisthine—no definite effect with asthma
TGB	50	F	200	Fairly good relief	Nil	Dust, cosmetics, lime and possibly food
LH	26	F	200	Moderate relief to rhinorrhœa otherwise nil	Pain in bridge of nose	No relief with antisthine or neo-antergan
ED	36	M	200 and 500 Average 100 prn	Good relief to nose	Nil	Rhinitis recurred on stopping hypsensitization because of a dermatosis
FZ	28	M	50 prn	Complete relief	Nil	More effective than antisthine
RT	12	M	150	Improved	Nil	Not asthmatic at time of trial
RS	15	F	50 prn	Good relief for 3 or 4 hours	None	Antisthine gave no relief—excellent relief with neo-antergan
RC	24	M	50 prn	Fairly good relief	Drowsy and dizzy	About equal to 100 mgm. antisthine in effect
KG	23	M	50 prn	Very effective	Very drowsy	Combined with 100 mgm. antisthine is most effective
WB	28	M	50 prn	Good relief	Nil	No relief with antisthine
RA	38	F	200	Good relief	Nil	Tree pollinosis. Asthma better but absence of tree pollen after likely explanation
MM	30	F	200	Good	Nil	No relief to associated asthma
JV	20	M	50 prn	Rapid and complete	Nil	No effect noted in asthma—seasonal exacerbation with tree pollen markedly benefited

TABLE X.  
PYRIBENZAMINE  
ASTHMA

Case	Age	Sex	Daily dosage	Results	Side effects	Remarks
MM	30	F	200	None	None	Good relief to rhinitis
AP	38	M	200	Cough improved?	Nil	Poor observer!
JV	50	M	50 prn	Nil	Nil	Good relief to rhinitis

URTICARIA

FJ	52	F	200	Nil	Headache, restlessness, insomnia	Insulin sensitivity
CBS	49	F	200	Good relief for several hours	Slightly drowsy	Acute urticaria probably food and drugs
WG	31	F	100	Rapid relief and disappearance of hives	Slightly drowsy	Cause unknown

ATOPIC DERMATITIS

ELA	58	F	200	Moderate relief to irritation	Nil	Eczematoid—long duration
HSS	59	M	200	Good relief to itching	Drowsy	Made him more drowsy than benadryl
FHH	32	F	50 prn	Good relief to itching	Nil	Cause not found
TO	35	F	200	Some relief to itching	Drowsy and felt weak	Huge anxiety factor
VH	28	M	50 prn	Marked relief	Nil	Better relief than with antisthine—nasal symptoms also relieved

clinical effect of antistine in this small group. At the present time I am making observations on the local use of the drug in the nose and on its use topically in an ointment but it is too early to report any results.

#### PYRIBENZAMINE

Pyribenzamine has been available to the profession in the United States for nearly a year and there are many published reports of its value.<sup>2</sup> It has only become available in Canada within the past two months. It is manufactured by the Ciba Company which kindly made a supply of this drug available to me in February, 1947. We have observed its effects on 26 allergic patients as summarized in Table VIII. While this series is too small to be significant my observations are comparable to other and larger published series.

As reported elsewhere toxic effects occurred in less than a third of the cases but all were mild and none were of the severity of those seen with benadryl on many occasions. Patients rarely complained of side effects and often these were only elicited on direct questioning. In one instance drowsiness was more marked than with benadryl. The one asthmatic showing marked improvement was sensitive to tree pollen and as tree pollinosis subsided about the time the drug was administered the results may have been fortuitous. In several cases relief was obtained when benadryl and antistine had been ineffective. In general when compared with antistine 50 mgm. of pyribenzamine was equivalent to 100 mgm. of antistine.

Eighty per cent of this small series gave a favourable response while only 61% did with antistine and benadryl. The toxicity of pyribenzamine and antistine was generally mild and occurred in 27 and 25% of cases respectively while it was noted in 60% of my previously reported benadryl series. It would appear therefore that pyribenzamine is the most generally useful drug of the three.

#### NEO-ANTERGAN

Neo-antergan was developed by Bovet *et al.* in France in 1944. It is a powerful antagonist of histamine in animal experiments and recently Feinberg and Friedlander have shown that in animals it is more effective than pyribenzamine. Clinically it has succeeded antergan, developed by Halpern in France in 1942. It is reported

to be more effective in allergic states and very much less toxic.

I received a very small supply for clinical trial in March, 1947, through the courtesy of Poulenc Frères. The limited amount and the short time available permitted its use in only six patients. In one asthmatic, it caused a severe exacerbation as had occurred previously when benadryl and later antistine were tried. In five cases of perennial hay fever marked relief occurred in four and none in the other. Apart from the development of severe asthma in the patient mentioned there were no toxic symptoms. In two instances relief was obtained where benadryl, antistine and pyribenzamine had failed to help. It was used in all cases in 100 mgm. doses as required.

#### DISCUSSION

My brief experience with these cases indicates that pyribenzamine is a potent antihistamine drug and that my observations are roughly parallel to those previously published. Toxic symptoms were noted in less than one-third of the cases in contrast with three-fifths of my benadryl cases<sup>1</sup> and the toxic symptoms were generally mild. As therapeutic effects occurred promptly in equivalent doses and in a similar number it was not surprising that patients often preferred pyribenzamine.

Antistine proved to have a definitely lower proportion of toxic side effects and was used generally in doses of twice that of the other drugs (100 mgm.:50 mgm.). However, it failed to give relief in as large a proportion of cases as pyribenzamine and in several instances failed to give relief when the latter drug succeeded.

Neo-antergan was used in too few cases to evaluate its effect but it would appear to be a valuable and relatively non-toxic drug.

Benadryl and the three drugs reported have similar pharmacological and clinical properties but vary greatly in their toxicity. In many instances one was helpful when the others were not or were too toxic. It is probably fortunate that these drugs are all available and can be chosen to suit a particular patient.

The antihistamine drugs are very effective symptomatically in urticaria, to combat itching in the allergic dermatoses, and in allergic rhinitis. I think that it is highly doubtful if they are of any value in asthma and they are sometimes dangerous. Some published clinical reports indicate benefit in a small proportion



of asthmatics especially with large doses. Such reports are probably open to question. If the asthmatic paroxysm is due to histamine the observed result should be prompt and this can be demonstrated experimentally. It seems likely that asthma is most frequently produced by acetylcholine or a related substance and that the antihistamines are therefore ineffective.

Again it would seem wise to sound a note of caution. All of these drugs are toxic in some degree and long continued use may prove to be dangerous. At best they are but palliative. Their effects are rapid but short and they do not cure.

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### NEW THERAPEUTIC APPROACHES IN ALLERGY\*

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THE attention of the medical profession has been drawn of late to allergic problems, by the introduction of several so-called anti-allergic drugs. This has aroused a hope in the minds of many of avoiding the bewildering maze of allergic management by a "therapia magna": a drug which will control all allergic problems by striking at the common root of all. I do not wish to become involved in the argument as to the feasibility of this approach, but only to say that I see no immediate possibility of such a solution of the problem. Nevertheless, the new drugs before-mentioned do give us considerable help in the management of some allergic symptoms.

Let us first sketch briefly the history of this development. It goes back to 1910, almost to the beginning of the allergic concept, when Dale and Laidlaw<sup>1</sup> noticed the resemblance between anaphylactic shock and histamine effect. Later, Lewis and Grant<sup>2</sup> pointed out that the whealing of urticaria could be duplicated by

injection of histamine. Other workers, (Bray,<sup>3</sup> Horton and Brown<sup>4</sup>), found that in allergy due to cold the symptoms were similar to those produced by histamine. The present concept, agreed upon by most workers, is that the antigen-antibody reaction which manifests itself in an allergic reaction, does so because of the liberation of histamine in the affected tissue, in amounts above the threshold of tolerance; histamine being at once the by-product of reaction, and the toxic agent whose effects are recognized as the allergic type-lesion, the wheal. This lesion manifests itself in different symptoms, depending upon its site, as urticaria, asthma, hay-fever, etc.

Now, if it were possible to restrain the production or activity of histamine, allergic symptoms would not occur. While this is actually an over-simplification of the problem (since the exact rôle of histamine is not agreed upon by all the students of the problem), much has been done to achieve the objective.

Naturally, in attempting to raise the tissues' tolerance to histamine, the first thing to be used was histamine itself. Injections in increasing doses have been reported by various workers, with a certain proportion of success, at least temporarily. Farmer<sup>5</sup> showed that histamine tolerance could be raised in guinea pigs, and by frequently repeated small doses he obtained effective results in asthma and vasomotor rhinitis. We have found that while temporary improvement may be expected in a certain number of cases of urticaria and asthma, the degree of improvement is usually not adequate, and is difficult to sustain. No satisfactory evidence of the production of anti-histamine antibodies has ever been adduced. This led Fell and associates<sup>6</sup> to attempt the conjugation of histamine and protein by an azo linkage in order to produce a haptene substance with immunizing properties. Using despeciated horse serum as the protein, they were able to reduce the mortality in guinea pigs to histamine shock from 52 to 8%. Sheldon and his associates<sup>7</sup> in 1941 reported on the clinical use of this substance, marketed as hapamine by Parke, Davis and Co. They reported good results in atopic and contact dermatitis in 8 of 17 cases, and in asthma, rhinitis, urticaria, etc., in 10 out of 22 cases. Other careful workers have made studies of the clinical use of hapamine, and at present most allergists who use it agree with Cohen and Friedman<sup>8</sup> that the degree of im-

\* Delivered at the Annual Meeting of the Ontario Medical Association, May 14, 1947.

munity conferred is not great, but that it serves as an adjunct in well-managed cases of allergy.

**Histaminase.**—Another approach to the histamine problem was offered by the work of Best<sup>9</sup> who demonstrated that bowel and kidney contain a substance capable of destroying histamine. This substance, called histaminase, was effective *in vitro*, but it was soon found that its effect *in vivo* was in most cases negligible. However, it is being used, and is at times effective in certain cases of allergy. Best and McHenry<sup>10</sup> in 1940 stated "For some years we have consistently answered numerous enquiries about histaminase with the statement that we believed there was no physiological basis on which to rest its clinical use".

A series of drug syntheses, reported first in 1933 by Fournneau and Bovet,<sup>11</sup> were carried on to a point where they announced that thymoxyethylene-diamine, or 929F, had the property of counteracting histamine activity *in vitro* and *in vivo*. This chemical proved to be too toxic for clinical use, and other syntheses resulted in new compounds of the series with increased anti-histaminic activity and decreased toxicity. The first of these introduced for clinical use was antergan (N. dimethyl amino ethyl-N-benzyl aniline) 2339RP in 1942, soon followed by neo-antergan (N-p-methoxy benzyl-N-dimethyl amino ethyl- $\alpha$ -aminopyridine) or 2786RP, Halpern.<sup>12</sup> Further research (in America) brought out benadryl (B-dimethyl amino ethyl benzhydryl ether hydrochloride), described as being more effective than antergan and neo-antergan, (Loew<sup>13</sup>). This preparation was supplied in 1945 by Parke-Davis to outstanding clinicians in the United States, and in 1946 was introduced to the profession for control of hay fever, and other allergic conditions. Reports on its effectiveness are now in the medical press, and its value is widely known. Mayer and his associates<sup>14, 15</sup> introduced pyribenzamine a little later, and while it is structurally different from benadryl, being pyridil-N'-benzyl-N-dimethylene diamine, its activity is found to be about the same in nearly all respects. Both drugs have a high safety range, but are prone to cause unpleasant side-effects, notably drowsiness, dizziness, nausea, and dryness of the mouth, nose and throat.

Antistine, the newest drug of this kind which has appeared, is the subject of reports (which I have read only in abstract), by Meier and Bucher,<sup>16</sup> Schindler,<sup>17</sup> Bourquin.<sup>18</sup> Its chemical

name is 2-phenyl benzyl amino methyl imidozoline. Since it was introduced to Canada less than three months ago, it has not been in use long enough to permit a full comparison with benadryl and pyribenzamine, but from a series of cases in which we have tried it, we find that it compares favourably with them in therapeutic effectiveness in parallel conditions. During the past few weeks we have treated 32 cases, for which reports are tabulated below:

Table I.

Diagnosis	Number of cases	Results		Reactions
		Good	Poor	
Asthma .....	4	1	3	1—dizziness, nausea
Coryza .....	9	5	4	2—nausea
Eczema .....	3	0	3	nil
Contact dermatitis. 2		2	0	nil
Urticaria .....	6	4	2	2—nausea
Pruritus .....	4	4	0	nil
Blepharitis .....	4	3	1	1—headache
Totals .....	32	19	13	6

The results as tabulated, show a strong similarity to those of benadryl and pyribenzamine, as reported in various papers. The more acute conditions, such as urticaria, pruritus, blepharitis, and contact dermatitis, where the histamine mechanism is a greater factor, are most beneficially influenced, whereas asthma, eczema and non-seasonal coryza, being determined to a larger extent by other factors, are less amenable to this type of treatment.

To my mind, the chief advantage of the use of antistine is the lower incidence of reactions; namely 18%, these being mild in almost all cases, and seldom requiring withdrawal of the drug.

A few typical case histories are appended.

## CASE 1

Mr. S.E.M., aged 36. Diagnosis seasonal coryza and asthma. Skin tests gave strong reactions to tree, grass, weed and fungus allergens. Specific hyposensitization advised. Seen April 29, coryza severe. Given antistine 100 mgm. q.3 h. Coryza stopped within a few minutes, no side-reactions observed. Asthmatic reaction followed next injection of pollen antigen; controlled by 100 mgm. antistine.

## CASE 2

Mrs. T.H.M., aged 50. First seen December 5, 1946, complaining of non-seasonal coryza of three years' duration. Skin tests: reactions to house dust and airborne fungus spores. Specific hyposensitization weekly. On April 3, 1947, reported attack of nasal irritation and coryza after attending a dog show. Antistine 100 mgm. q.4 h. prescribed. Reported later that symptoms were controlled within thirty minutes, effect lasting three hours; no side-reactions.

### CASE 3

Mrs. J.B., aged 24. Urticaria following penicillin administered for osteomyelitis of radius. March 1, 1947, antistine 100 mgm. solution subcutaneously, and antistine 100 mgm. tablets by mouth q.4h. March 3, 1947 reported urticaria controlled for three hours after each tablet. After combing hair small lumps appear, but not so large or irritable as before. March 6, 1947, no further urticaria. No reaction at any time.

### CASE 4

R.D., aged 25. Severe dermatitis, of hands and forearms, occupational and medicamentous, treated with compresses of aluminum acetate. March 1, 1947, antistine 100 mgm. q.3h. plus antistine 100 mgm. ampoule subcutaneously twice a week. Dramatic relief of itching and recovery followed. Back to work March 18, 1947. No reaction.

### CASE 5

Mrs. E.M., aged 53. Complaint pruritus ani, treated previously by injections of local anaesthetics, hæmorrhoidectomy, etc., without relief. Skin tests negative. Given antistine 100 mgm. q.4h. Through a misunderstanding of directions tablets were taken at 15 minute intervals for several doses. The patient reported the first relief she had had for twelve months, this relief being complete for 24 hours. When tablets were taken as ordered, one every four hours, symptoms were kept under control until she left recently for a visit to Alberta.

In reviewing these case histories, I would like to stress the point that this medication is not being used as a cure for allergic conditions, its chief place in treatment seems to be in controlling acute symptoms of coryza and itching, with the minimum of side-effects. It seems to do this by its specific effect on histamine in the tissues. Since histamine is only one factor in the allergic reaction, it is not to be expected that it will take the place of thorough allergic study and management, such as has been always necessary in the treatment of allergic cases.

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Medical Arts Bldg.

### RÉSUMÉ

Revue des principaux agents thérapeutiques anti-histaminiques, notamment, appréciation des résultats obtenus avec le bñadryl, la pyribenzamine et l'antistine. Cette mñdication agit momentanément, avec ou sans réactions notables, sur les effets fñcheux dñs à l'intolérance de l'histamine mais elle n'agit que sur cet élément du mécanisme allergique. Puisque cet élément n'est pas unique, il faudra continuer de poursuivre la recherche des autres mécanismes pathogéniques des manifestations allergiques.

JEAN SAUCIER

## BIOCHEMICAL CHANGES IN HYPERTENSION\*

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RECENT work has brought forward the possibility that the adrenal cortex through its influence on electrolyte metabolism may be a factor in the pathogenesis of such "idiopathic" vascular diseases as rheumatic fever, hypertension and nephrosclerosis, and periarteritis nodosa.<sup>1</sup> Other studies have demonstrated changes in electrolyte excretion in hypertension<sup>2</sup> and recent clinical studies have suggested that the outmoded treatment of hypertension by low salt diet may be very valuable.<sup>3</sup> There is also considerable evidence on the production of hypertension in cases of Addison's disease overtreated with desoxycorticosterone acetate. Perera *et al.*<sup>4</sup> have demonstrated that even in normals such treatment will cause an increase in blood pressure.

The present study was undertaken in an attempt to assess the part played by the adrenal cortex in essential hypertension. There are, however, many limiting factors in such a study. Morphologic changes in the adrenal reflect only the most gross physiological disturbances, and a recent case of metabolically indisputable Cushing's disease has been reported with histologically normal adrenals and pituitary.<sup>5</sup> Urinary assays for the end products of adrenal cortical metabolism, while useful for testoid and glyco-corticoid excretion, have as yet failed to measure mineralo-corticoid factors, and it is with these that any derangement in electrolyte metabolism must be related.

It had been demonstrated that in desoxycorticosterone-treated animals which developed rheumatism, hypertension and nephrosclerosis, one of the most consistent findings was an in-

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other disease except the hypertension, which in many cases was asymptomatic and had been discovered on routine physical examination, and those with nitrogen retention or in cardiac failure were discarded from the series. None of these 38 patients had been sympathectomized. Ophthalmologic examination, urea clearance, urine concentration tests, chest x-ray and electrocardiographic studies were carried out in all cases.

Table I, shows the findings; 17 normal and 38 hypertensive Na/Cl ratios were plotted against diastolic blood pressure. It will be seen that with an increase in diastolic pressure there was an increase in Na/Cl ratio, and that there are no patients in whom an increased ratio was present with a normal blood pressure. There were however a number in whom the converse was true, *i.e.*, a normal ratio in the presence of a high diastolic pressure. Fig. 2, shows the Na/Cl ratio in relation to both age and diastolic blood pressure, demonstrating that an increased ratio was more frequent in the younger age group, especially in those with diastolic pressures above the group average.

TABLE II.

	Diastolic B.P.	> 116	Na/Cl	
			incr.	not incr.
Under 50 years of age	< 116	1	10	
Over 50 years of age	> 116	1	3	
	< 116	0	7	

In 18 of the patients, glyco-corticoid and 17-ketosteroids were determined, the former by the method of Venning<sup>8</sup> and the latter by the Holtorff and Koch method. Normal glyco-

corticoids are 40 to 90 glycogen units in males, 25 to 65 in females, while 17-ketosteroids values are 10 to 25 mgm. per 24 hours in males, and 8 to 18 mgm. per 24 hours in females. It will be noted from Table III that while the hypertension range was apparently identical in the males and females there was only 2 high glyco-corticoid value among the females, and these are both in patients previously suspected of having Cushing's disease. There were invariably low 17-ketosteroid values in those patients with increased glyco-corticoids, as well as in some of the others. This confirms the previous findings of Bruger *et al.*<sup>9</sup> Interpretation of these data is impossible at present.

In the course of taking the histories on these patients, careful inquiry was made for rheumatic fever. In 30% of the patients under 50 years of age (15 of 45 patients) a frank history of an episode of febrile arthritis, apparently rheumatic fever, was obtained. If patients who had had such vague but suggestive complaints as "growing pains", "rheumatics" and transient arthralgias were included the percentage was increased to 50%.

#### THERAPY

Over a period of 2½ years all hypertensive patients coming to our clinic, regardless of biochemical findings or previous sympathectomy, were treated with 6 gm. daily (1½ gm. t.i.d.p.c. and h.s.) of an especially coated ammonium chloride,\* unless there were contraindications for such therapy (uræmia, acidosis, intolerance). A control period on placebo tablets, identical in appearance with the ammonium

\* Dalitol—Frank W. Horner Ltd., Montreal, Canada.

TABLE III.

Patient	Blood pressure	Age	Sex	17-KS	Glyco-corticoids	Na Cl
Be. ....	210/120	55	M.	6.0	53	
Ch. ....	180/100	36	M.	9.9	(toxic extract)	1.33
Do. ....	227/130	49	M.	10.2	117.2	1.41
Ke. ....	210/87	56	M.	6.2	201	
Ha. ....	250/150	39	M.	6.0	184	1.55
Bo. ....	210/110	59	M.	13.8	91	1.43
Ry. ....	262/140	42	M.	8.6	134	1.38
Wa. ....	180/112	40	M.	18.8	58	1.41
Co. ....	200/110	51	M.	5.3	43	
Hr. ....	200/140	43	M.	8.8	72	1.48
Du. ....	180/100	14	F.	6.1	82	
Ha. ....	190/120	43	F.	3.6	45	1.41
La. ....	190/110	33	F.	13.5	45	1.30
McK. ....	240/140	25	F.	15.6	51	(1.30) uræmia
Sm. ....	230/100	46	F.	12.0	53	1.38
Si. ....	190/90	47	F.	6.7	63	1.32
Do. ....	220/150	42	F.	4.7	42	1.85
Ar. ....	220/140	33	F.	4.6	126.0	1.52

Values in italics are considered abnormal.

chloride, preceded treatment in all but two cases, the urgency of whose condition impelled us to begin therapy at once. Such placebo administration was continued until the blood pressure had reached an apparently stable basal level under clinic conditions, a period usually lasting 3 to 6 weeks. During this time the patients acquired confidence, knew the clinic personnel and were no longer under their initial tension. In a few patients it was difficult to establish the end of this period since their blood pressure fluctuations from week to week were so great; these initially, and all our patients subsequently, were admitted to hospital for one night where a sodium amytal test was carried out (3 grains by mouth at hourly intervals for 3 hours, blood pressure taken every  $\frac{1}{2}$  hour until it returned to its initial level). These tests were then repeated every 2 to 3 months, and the response to therapy was judged accordingly. If there was no change after 6 to 8 months, treatment was considered ineffectual; or if after an apparent drop in pressure, replacing the ammonium chloride by placebo did not cause a rise, they were judged not to have responded.

TABLE IV.

	Response to $NH_4$ Cl therapy	
	> 1.44 Na/Cl	< 1.44 Na/Cl
+	4	4
$\pm$	0	2
0	0	4

Many patients were of course started on therapy who disappeared from the clinic, or who followed treatment so intermittently as to be ineligible for consideration under these criteria. In most cases at least a year was necessary for the adequate judging of any therapeutic response in such an unpredictable disease. Table IV shows that among the patients meeting such standards, responses were better among those with increased ratios than among the normal ratios, although we have seen several excellent results in people whose initial ratio was normal. It can be said with some certainty that no favourable responses were seen in any patient over the age of 50 years whose diastolic pressure was less than 100 mm. Hg., regardless of the height of the systolic. This group presumably represents the arteriosclerotic patient whose high systolic pressure is on the basis of an inelastic aorta.

## DISCUSSION

In considering these data, we felt that the the most significant finding is the total lack of patients having a high Na/Cl ratio in the presence of a normal diastolic pressure. The fact that there are many hypertensives with normal ratios may be interpreted in several ways; either this group may represent a different type of hypertension (neurogenic?), or it may mean that such patients are no longer actively hypertensive and have a high blood pressure, which is the result of renal damage in a previously active phase. It could also represent a technical error, since if the serum is not separated promptly from the cells after clotting the rise in serum Cl will be sufficient to decrease the ratio to normal limits.

Since some cases of Cushing's disease show the same biochemical picture, we were interested to discover that a patient with very high (400 to 700 glyconic units) glyco-corticoid excretion and the typical striae and facies, polycythemia, etc., but lacking the hypertension, did not have an increased Na/Cl ratio.

We have had two patients with normal Na/Cl ratios who, having failed to respond to ammonium chloride therapy responded well to subsequent sympathectomy. We have also seen a number of sympathectomized patients whose hypertension had been unaffected by operation, but who showed considerable improvement with ammonium chloride. Optimal cases for sympathectomy appear to be those whose blood pressure is still labile, who show pronounced falls in blood pressure with Na amytal, tetraethyl ammonium chloride, spinal anæsthetic, etc. The converse is to some extent true of ammonium chloride therapy in that our best responses have been in patients with apparently fixed diastolic blood pressure, patients who would be classified as "malignant" or "sub-malignant" types. It has been our impression also that the patients who have had previous rheumatic fever have responded to ammonium chloride even when their ratios were normal.

It would appear that failure of blood pressure to increase on placebo after ammonium chloride on one occasion does not necessarily imply a similar response on another. One recent patient failed to show a rise on the first occasion but after another few months of ammonium chloride showed a marked rise when again given placebo (140/80 to 240/130 within 3 weeks, where it was maintained for another



2 weeks on placebo). We interpret this as indicating that on the second occasion she was in an "active" or ascendant phase of the disease. Again given ammonium chloride her blood pressure dropped steadily but at a much slower rate than its ascent, requiring from 10 to 12 weeks to reach the previous low level.

One case history of a 39-year old Nova Scotia miner seems worth giving in some detail

He had been perfectly well until August, 1945, when he developed "grippe". Following this, he had gone to his physician asking for a check-up because he was feeling run-down and because he wanted to get married. At this time a urine examination was normal, although a blood pressure was not taken. Several weeks after this he noticed that his right shoulder was tender and painful, and a week later this rheumatism had shifted to his left shoulder. Within another week it had disappeared. By November, 1945, he was complaining of headaches, loss of vision, dizziness and was admitted to the Montreal Neurological Institute with a blood pressure of 250/150. His fundi showed papilloedema, exudates, and hæmorrhages though little arteriolar sclerosis. His urine contained +++ albumin, casts and a few red cells. He was afebrile, sallow and appeared very ill. Electrocardiogram showed very few changes, heart size by x-ray was normal. His Na/Cl ratio was 1.55, his CO<sub>2</sub> combining power 72 vol. %. Non-protein nitrogen was normal.

TABLE V.

	B.P.	DEC. 1945	JAN. 1946	MARCH 1946	AUG. 1946	MARCH 1947
AVERAGE B.P.	250					
COLD PRESSOR RESPONSE	200					
NA AMYTAL TEST	150					
FUNDI	100	++++	+++	++	0	0
URINE ALBUMIN	50	+++	+++	0	0	0
MAXIMUM CONC.	0	1.014		1.024	1.012	1.022
NA/CL		1.55				1.38
GLYCO-CORTICIDS		153	100	108	137	49.2
17-KETOSTEROIDS		160	184			
		9.2	6.0	6.9	7.2	12.2
R: 6 gm NH <sub>4</sub> Cl qd.						

Because of the biochemical findings, he was placed on ammonium chloride for a trial period. Since we had had some doubts about absorption of enteric-coated tablets, careful search of three stool specimens was made for undigested pills and none were found. He seemed however, to be having no response to treatment, not even what would be expected from the diuretic properties of the drug, and after 10 days another CO<sub>2</sub> was taken, which was unchanged, indicating conclusively that he had absorbed none of the tablets although they had been digested. Since his vision was almost entirely gone and he had had several fresh hæmorrhages involving the macula of one eye, it was felt that some treatment was immediately necessary which would relieve his hypertension, even if

only transiently. The neurosurgeons were loath to operate, but on the advice of the medical service performed a supradiaphragmatic sympathectomy (Peet operation). Within 4 days postoperatively his blood pressure had reascended to 180/120 (January, 1946), and although his vision was improved and he felt better, his wife was told that the prognosis was hopeless. Before sending him home however, we placed him on 6 gm. a day of ammonium chloride, this time putting it into gelatin capsules. He continued treatment and returned to Montreal in March, 1946, August, 1946, and March, 1947. Changes in his condition are shown in Table V. He has been at work since March, 1946, is asymptomatic and his fundi are normal except for the pigmentation around the old macular hæmorrhage. His vision has improved steadily since the onset of treatment.

It will be noted from Table V, that his blood pressure drops were shown both by his sodium amytal and cold pressor tests, and at the end of treatment his highest level on cold pressor test was not as high as his lowest value with Na amytal before treatment. It will also be seen that he continued to show increased urinary corticoids until the last admission when for the first time all findings were normal.

Interpretation of this case is difficult but it seems possible that the grippe evoked an abnormally great adrenal response causing his hypertension and the concomitant biochemical changes, and that this hyperactivity was nullified (as in the experimental animals on desoxycorticosterone) by the ammonium chloride. In the course of 18 months the hyperactivity had dissipated itself, and his adrenal function was again normal. There are however a number of unanswered questions. (1) In spite of the opinion of the neurosurgical department that he was unsuitable for operation and a postoperative failure, and even in the face of the rapid postoperative blood pressure rise and the limited sympathectomy, we do not know whether there may not have been a synergistic relationship between the operation and the medication. Nor (2) do we know what will happen to this patient when he is next exposed to some damage to which the adrenal will respond, perhaps exacerbating his hypertension.

Of our other patients followed for as long as this who have had a good response to therapy, none were as acute and therefore assessment of improvement is more difficult. One other patient whose history indicates that his hypertension was probably not of more than 1 to 2 years' duration, with papilloedema and similar urinary findings in hormone excretion, is showing a similar response to therapy and has not been operated upon, but he has only

been followed for 8 months at the present time; in this interval his lowest reading on sodium amytal administration has dropped from 174/112 to 140/100, and his papillœdema has improved markedly. All other cases would be classified as "essential hypertension", the duration of which is impossible to estimate.

#### CONCLUSIONS

1. In some hypertensives there is an increase in the ratio of serum Na to Cl, expressed as Na/Cl, which is apparently never found in patients with a normal blood pressure, and which may be related to an abnormal adrenal cortical hormone production.

2. Thirty per cent of the hypertensives in this series, under the age of 50, give a previous history of one or more episodes of febrile arthritis, diagnosed in most cases as rheumatic fever.

3. Some hypertensive patients show an increased glyco-corticoid urinary excretion and this is accompanied by a decrease in urinary 17-ketosteroids.

4. In patients showing an increased Na/Cl ratio, as well as in some not showing it, encouraging results have been obtained with ammonium chloride therapy.

The author is greatly indebted to a number of people who have co-operated in this effort: Dr. Eleanor H. Venning who did the cortical hormone assays in the urine; Drs. D. L. Thomson and J. S. L. Browne for their kind advice on many biochemical matters; The Commonwealth Foundation for partially supporting this work; Frank W. Horner, Ltd. for supplying both ammonium chloride and placebo, and to Dr. H. Selye for supplying the author's time.

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Mankind have a great aversion to intellectual labour; but even supposing knowledge to be easily attainable, more people would be content to be ignorant than would take even a little trouble to acquire it.—Samuel Johnson.

## IODINE DEFICIENCY DISEASE

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OF medicine's great indebtedness to the investigations of physiologists on the experimental behaviour of laboratory animals we are, as physicians, well aware; of the valuable data that are to be found in the reports of veterinarians and others associated with domestic livestock we are much less aware and to our professional loss. In this regard the lesson taught by veterinarian science in respect to iodine deficiency disease is an excellent example.

#### IODINE PROPHYLAXIS IN DOMESTIC ANIMALS

For many years prior to 1907 the livestock ranchers of the United States and Canada resident in goitre areas experienced great difficulty in obtaining viable offspring from their ewes, cows, mares and sows. In 1907, when iodine containing-salts were first fed to sheep in Michigan in an attempt to prevent the high death rate then prevalent among the new born lambs of that and other goitrous States, the first practical measure was taken in the prevention of an economically devastating form of iodine deficiency disease, the neonatal deaths and stillbirths.<sup>2</sup>

In 1916, the stock raisers of Montana, were faced with a ruinous mortality among their new-born livestock, together with the development of goitre and underfunction of the thyroid glands of their domestic animals. The administration of iodine containing-salts to their livestock remedied this condition to a large degree. Similarly, at the University of Wisconsin Farms, after the introduction of iodized salt in 1920, there has not been any instance of goitre among the domestic sheep, swine, colts and calves.<sup>3</sup>

Many Canadian physicians will recall the notable report of W. D. Keith made at the C.M.A. Meeting in Victoria in 1926. On that occasion we were informed of the interesting experiences of the stock raisers of Pemberton Meadows in the valley of the Lillooet River, ninety miles north-east of Vancouver. The white settlers in this fertile valley were on the verge of economic ruin occasioned by the remarkable fact that 80 to 90% of all livestock, foals, calves, pigs, were dead at birth or died shortly afterwards. Disaster was only averted, and then very completely and dramatically, when, on advice from Marine, iodine was put into the drinking water of the pregnant mares, cows and calves.

This form of iodine deficiency disease, known as "fetal athyrosis", has been seen and is now prophylactically controlled in other goitre areas including Minnesota, North and South Dakota, Wyoming, Washington, Idaho and southern Alberta.<sup>5</sup>

From a consideration of the above data it can be concluded that iodine deficiency disease in domestic animals is shown by a marked lack of viability in the new-born. That this disease is entirely preventable by the administration of iodine to the pregnant livestock there can be no reasonable doubt.<sup>1</sup>

#### STILLBIRTH IN HUMANS A MANIFESTATION OF IODINE DEFICIENCY DISEASE?

Syphilis<sup>6</sup> and cerebral hæmorrhage<sup>7, 8</sup> are no longer regarded as important causes of stillbirth. The question arises, are human stillbirths, like their animal counterparts, a manifestation of iodine deficiency during pregnancy?

In this connection I have reported<sup>9</sup> concerning the results of a clinical study made in Vancouver, in the Pacific North-West goitre belt. In this study the birth statistics of the city of Vancouver were considered in two separate series: (1) those births occurring in the city at large in the years 1925 to 1929 inclusive, and, (2) deliveries in the Maternity division of the Vancouver General Hospital during the three year period from 1930 to 1932 inclusive.

The identity of physicians who routinely administered iodine to their pregnant patients was obtained by personal inquiry. The recorded births were scrutinized and all instances of stillbirth were tabulated. When the attending doctor could not suggest any reason for the stillbirth, the latter was classed as unexplained or "idiopathic". If, on the other hand, any possible physical cause of stillbirth existed such as dystocia in primipara, breech delivery, prolapse of the cord, cord-around-the-neck, etc., the case was not included in the idiopathic category. In the second series the records of the Vancouver General Hospital ensured real accuracy in screening the idiopathic stillbirths.

The first series included 19,730 deliveries occurring in the city of Vancouver in the five year period from 1925 to 1929. In this series there were 330 stillbirths (1.67%) of which 91 were considered idiopathic. In 2,252 deliveries of women to whom iodine had been administered prenatally there were only 2

instances of idiopathic stillbirth, an incidence of 0.089%. In the remaining 14,528 deliveries in women receiving no prenatally administered iodine there were 82 idiopathic stillbirths, an incidence of 0.56 %. To summarize, when the mother did not receive a special quota of iodine during pregnancy there were 6.33 times as many idiopathic stillbirths as occurred in patients receiving iodine prenatally.

The second series included all patients delivered in the Maternity Division of the Vancouver General Hospital between 1930 and 1932 inclusive. In this series there were 4,813 deliveries and 135 stillbirths; of the latter, 50 were idiopathic. In the deliveries of 741 women who received iodine prenatally, there were no instances of idiopathic stillbirth, while during the same period, and under the care of equally capable obstetricians who did not prescribe iodine prenatally, there were 49 idiopathic stillbirths, an incidence of 1.22%.

In the five year period from 1925 to 1929 the incidence of stillbirths in Canada was 3.09%, in British Columbia 2.73% and in the Indians of British Columbia it was 1.26%, about one half of the figure for the white populace. In the Indian deliveries a doctor was in attendance less than half the time. It would appear that the iodine-rich diet of the Indians (largely sea food) helped to diminish the incidence of stillbirths. It is of interest to note that the duration of labour in an Indian primipara is between 12 and 16 hours.<sup>10</sup>

Abbott and Ball<sup>11</sup> in Manitoba made a study of the thyroid glands of stillborn fetuses and newborn babies who died shortly after delivery. In a series of 100 consecutive autopsies they reported that 41% had anatomical evidence of disease in the thyroid gland.

From a consideration of the foregoing data it would appear to be probable that, stillbirth in humans, like its prototype in domestic animals, is a manifestation of iodine deficiency.

#### RELATIONSHIP OF IODINE DEFICIENCY TO THE GENERAL HEALTH

It has been shown<sup>12</sup> that normal somatic growth depends upon the ingestion of adequate quantities of iodine. Boys receiving sufficient dietary iodine in a goitre district grew, on the average, 7 mm. more in height than untreated controls over a period of one year; they increased their weight by 200 gm. over controls receiving no supplementary iodine. In this



study it was also found that the average birth weight of infants whose mothers received prenatal iodine was 100 gm. greater than that of control infants.

It has also been shown that the feeding of milk with an increased iodine content to children living in a district with a high incidence of goitre resulted in more rapid and regular growth and development. Children with debility or showing impaired development or retarded growth showed steady improvement when iodine-containing milk was ingested.<sup>13</sup> The direct feeding of iodine to the young was also found to be beneficial.<sup>14</sup>

*The human requirements of iodine.*—The optimal daily requirement is approximately 200 micrograms for an individual weighing 154 pounds.<sup>15</sup> During pregnancy and lactation extra quantities are necessary in the dietary.<sup>16</sup>

#### CONCLUSIONS

Dietary iodine deficiency is a well known cause of stillbirth and neonatal death among the livestock in goitre districts of North America.

Dietary iodine deficiency is probably a potent factor influencing the incidence of stillbirth and early neonatal death in humans inhabiting a goitrous area.

The addition of iodine to the diet of young animals and children living in a goitre belt increases their growth and development.

The supplementation of the diet by iodine of humans living in a goitrous area, during pregnancy and lactation, is indicated in the interests of both mother and offspring.

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#### EFFECT OF MALARIA ON PREGNANCY

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THIS report is a study of the effect of malaria on the course of pregnancy based on the admissions from May 1, 1946 to end of April, 1947, to the Obstetrical Department of the Kweilin Provincial Hospital. Our admissions totalled only 360 cases but in spite of the relatively small number involved, we felt we were justified to undertake this study.

The Province of Kwangsi and also its capital Kweilin is one of the worst malaria-infested regions in China. No accurate statistical data are available but sources of long experience and good judgment estimate that at least 50% of the population suffers from malaria. Our figures are in favour of this opinion. Its effect on pregnant women exhibits itself in several ways. It causes a large proportion of abortions, it precipitates premature labour with corresponding danger to the child, and last but not least it may present difficult diagnostic problems.

In spite of the immense number of malaria cases throughout the world there have been comparatively few studies on its effect on pregnancy, labour and puerperium. To illustrate lack of interest in this field it may be mentioned that DeLee in his wellknown obstetrical textbook does not mention malaria at all. We feel this problem deserves more interest. High fever in labour or puerperium is a shocking experience to all of us; and those who have had to decide on the management of a febrile puerperium will recall what a relief is a positive laboratory report on a blood smear. Possession of penicillin and the knowledge that puerperal sepsis and malaria can coexist will not change much of this statement's value.

*Incidence.*—The health organization of the League of Nations in 1932 gave a conservative estimation of 300 million cases of malaria throughout the world. (1) This would include about 10 million pregnancies affected with malaria unless chronic malaria would con-

siderably reduce the rate of conception, of which we found no evidence in the literature. (2) Cecil estimates one million cases in the United States, which will no doubt increase on the return of veterans from malaria-infested regions of military operations; 100 million are estimated in India and a great part of the remaining 200 million or more is found undoubtedly in China.

In our series (see Table I) we had 59 cases proved to be positive on laboratory examinations which represents a percentage of 17% of the total admissions. On the other hand there were 173 cases of definite malaria past history, which amounts to 48% of our total admission. We had 8 cases treated on clinical signs only. For definite and lasting experiment only proved cases should be counted. We included those cases with malaria history for the purpose of evaluating the effect of chronicity or as past history as such.

TABLE I.  
SHOWING NUMBER AND PERCENTAGE OF ADMISSIONS  
TABULATED ACCORDING TO LABORATORY FINDINGS,  
PREVIOUS MALARIA HISTORY AND CLINICAL SIGNS

Classification of cases	Admission	
	Number	Percentage
Plasmodium positive .....	59	17
Malarial past history, plasmodium negative .....	173	48
Negative past history, negative laboratory finding .....	120	33
Clinically suspect without past history or laboratory findings. Received antimalarial treatment	8	2

#### EFFECTS OF PREGNANCY

Standers<sup>3</sup> begins his short description of the effect of malaria as follows:

"Despite the somewhat widespread opinion to the contrary it would appear that the ordinary forms of malaria have but little influence upon the course of pregnancy, although Goth<sup>4</sup> has reported 19 out of 46 cases ended in premature labour."

In our series (see Table II) we had 19 premature and 9 threatened or incomplete abortion cases out of 59 proved malaria cases. This figure rather corresponds to Goth's<sup>4</sup> report; 48% of abnormal cases certainly constitute an alarming figure if compared with 18% of abnormal admissions in the so-called malaria free group.

The cause of interruption of the pregnancy is variously given as the reaction to the high fever (Titus<sup>5</sup>), or to uterine contractions caused by the plasmodia and partly to premature separations as mentioned by Jaschke<sup>6</sup> and Pan-kow in their textbook. Another reason is given by DaLeas, who believes the fetus will become infected very frequently, which is then almost always followed by abortion. Manson-Bahr<sup>8</sup> mentions that "malaria *per se* is a far more potent oxytocic than any drug". He then continues:

"Intra-uterine death of the fetus is fairly frequent, whilst clinical and pathological evidence points to malaria as a powerful predisposing factor in the toxæmias of pregnancy, such as pre-eclampsia, eclampsia and nephritic toxæmia."

We noted the number of cases with albuminuria and œdema; and as is shown in Table VI, there is only a moderate increase in percentage as compared with the free cases. Wickramasuriya's report of 40% of general anasarca out of 357 cases especially investigated in pregnant women is probably due to malnutrition rather than to the specific effect of malaria.

That albuminuria and œdema of renal origin occur in tropical malaria is well established. Hypertension is also often noted. Snapper<sup>10</sup> reports a case where tertian malaria was the cause of acute nephritis. Nephritis predisposes to toxæmia, so malaria can be regarded as a predisposing factor as Manson-Bahr<sup>8</sup> mentions. As in our 59 cases no definite toxæmia occurred

TABLE II.  
SHOWING COURSE OF PREGNANCY AND COMPLICATIONS GROUPED AS IN TABLE I

	Total No.	Full term		Premature		Threaten.		Abortion Incompl.		Total abnormal cases	
		No.	%	No.	%	No.	%	No.	%	No.	%
Plasmodium positive .....	59	31	52	19	32	7	12	2	4	28	48
Malarial past history, plasmodium negative ....	173	140	81	19	11	7	4	7	4	33	19
Negative past history, negative laboratory finding .....	120	99	82	15	13	1	1	5	4	21	18
Clinically suspect, no past history, negative lab. finding. Antimalarial treatment ..	8	5	62	0	0	3	38	0	0	3	38

it is unlikely that malaria is such a powerful factor in the etiology of toxæmias.

*Type of infection.*—We investigated the comparative effect of falciparum to vivax infection. As is shown in Table III, there were 33 cases of falciparum as against 26 cases of vivax infections. Falciparum infections are apt to cause pernicious symptoms and according to Manson-Bahr<sup>8</sup> and others it is especially true in cases of pregnancy. He calls attention to cerebral manifestations which may come unexpectedly, without any previous malarial history and may cause serious diagnostic difficulties. We had no pernicious cases. Although in general in our cases falciparum infection caused the same percentage of abnormality as vivax infections, they caused a considerably higher number of stillbirths as is shown in Table VII. We had one case of double infection; it was a case of incomplete abortion. There were no quartan malaria cases.

TABLE III.  
SHOWING DISTRIBUTION AS OF SPECIES OF PLASMODIUM

Species	Number of cases	Percentage
Plasmodium vivax .....	26	44.3
Plasmodium falciparum .....	33	55.7
Total .....	59	100.0

TABLE IV.  
EFFECT OF MALARIA AS OF THE SPECIES INVOLVED

	Total	Full term	Premature	Abortion			
				Threaten.	Incompl.		
	No.	No.	%	No.	%	No.	%
Plasmodium vivax .....	26	14	54	6	23	5	19
Plasmodium falciparum .....	33	17	52	13	39	2	6

TABLE V.  
COMPARATIVE RESULTS OF KAHN TEST (BLOOD)

	Number of cases	Positive	
		No.	%
Plasmodium positive .....	52	6	11
Malarial past history, negative laboratory findings .....	142	10	7
Negative past history, negative laboratory findings .....	83	11	13
Clinically suspect without past history or lab. findings ..	6	0	0

TABLE VI.  
SHOWING NUMBER AND PERCENTAGE OF CHILLS, ALBUMINURIA AND CEDEMA

Classification	Total admission	Chills		Albuminuria		Edema	
		No.	%	No.	%	No.	%
Plasmodium positive							
Vivax .....	26	5	19	2	8	3	12
Falciparum .....	33	7	21	8	24	5	15
Total .....	59	12	20	10	17	8	13
Malaria past history, negative laboratory findings	173	3	2	30	17	19	11
Cases with no malaria past history, laboratory or clinical findings .....	120	5	4	24	20	7	6

*Effect on the product of gestation.*—High percentage of abortion and premature labour will naturally carry high fetal mortality. We had (see Table VII) 18.5% of stillborn and aborted cases as against 9% in the malaria free cases. We also had 10.2% premature babies against 5.8% in the free cases; a great proportion of them will very probably not survive.

The factor of intra-uterine fetal infection should also be considered. This question of congenital malaria gave rise to several conflicting statements and reports. Titus<sup>5</sup> cites Blacklock and Gordon<sup>11</sup> who “advanced evidence against the suggestion that malarial infection of the fetus takes place”. The fact that Blacklock and Gordon could not find plasmodium in the fetal blood cannot be accepted in face of positive findings by Schwartz<sup>12</sup> in 6% of the cord-blood and 3.6% of the blood of the infants out of 56 negro women examined in Central Africa. Placental infection on the other hand was shown in 74% in his cases, which made him believe that congenital malaria is of very little importance. Wickramasuriya<sup>9</sup> and DaLeas<sup>7</sup> state fetal infection is more often the cause of death than formerly believed. Chen, Tang and Wang<sup>13</sup> report 39 cases from the literature and

one of their own. We had no opportunity to investigate this phase of the problem but after studying related publications and following some of our cases we believe in the occurrence of congenital malaria.

*Effect of malarial past history.*—Cases with malarial past history but negative plasmodium report on admission were tabulated separately in order to see whether the presence of a



TABLE VII.  
COMPARISON SHOWING CONDITION OF PRODUCT OF GESTATION

Classification	Healthy		Premature		Stillborn		Aborted		Pregnancy carried	
	No.	%	No.	%	No.	%	No.	%	No.	%
Plasmodium positive										
Vivax .....	14	53.8	0	0	3	11.5	3	11.5	6	23
Falciparum .....	19	57.5	6	18.2	5	15.1	0	0	3	9
Total .....	33	55.9	6	10.2	8	13.5	3	5	9	15.2
Malaria past history, neg. lab. findings	142	82	3	1.7	6	3.5	9	5.2	13	7.5
Cases with no malaria past history, laboratory or clinical findings ....	101	83.9	7	5.8	7	5.8	4	3.3	1	0.8

malarial past history has any effect on the course of pregnancy. We had 173 cases, 48% of total admission. It appears that a past history as such has no adverse effect except in the possibility of recurrency. Vivax malaria may be expected to relapse in 55%, falciparum in 45% of the treated cases (Mackie, Hunter, Worth<sup>1</sup>). One wonders whether the so-called suppressive malaria medication would not be worthwhile in order to prevent complications. In our 59 cases 50 were recurrences and only 9 primary infection. A major part of the recurrent attacks could have been prevented and no doubt most of the premature labours would have continued to full term and some of the stillborns born alive. The author has not heard of any investigation in this line; it is hoped this possibility will be explored in the near future.

*Clinically suspect malaria cases and pregnancy.*—Stander<sup>3</sup> says in his textbook: "Too many sins of omission and commission on the part of the obstetrician have undoubtedly been cloaked under the diagnosis of malaria" and continues "the existence of malarial fever should not be entertained until all other possibilities have been practically eliminated and the characteristic parasites have been found in the blood." There is no question of the advisability of a most thorough search for the cause of any fever; but one perhaps should not delay such a relatively harmless medication as atabrine or quinine where there is considerable clinical suspicion of malaria. Imperati and his co-workers<sup>14</sup> have depended as often on the leucopenia and relative mononucleosis of malaria as on the actual finding of the parasite in the blood. We had 8 cases of such a nature and we were convinced of having been right in initiating anti-malarial treatment.

*Some other observations.*—Chills had occurred in 20% of the plasmodium positive cases; 3%

of all the other cases showed chills during their hospitalization.

Red cell count per c.mm. averaged 3,680,000; for the clear cases 3,820,000, and for those with past malarial history it averaged 3,720,000. The difference does not justify special comment except to note that it was quite low in all categories, which in itself makes complications more serious and prevention more important.

White cell count averaged 8,960 per c.mm. as against 9,610 in the malaria-free cases.

Results of Kahn tests. Cecil<sup>2</sup> mentions that "sometimes" in malaria a false positive reaction was obtained. Potter<sup>15</sup> tested 100 men with malarial infection, who all had previously negative Wassermann and Kahn test and were presumably free from syphilis, and found 12 positive and 10 doubtful cases. They all became negative within 30 days. Rosenberg<sup>15</sup> made a study to determine which serological test would give the smallest percentage of false positive reactions in malaria. Hinton test was found to be most reliable and Rosenberg advises to suspect syphilis if a positive reaction persists beyond 6 weeks in the absence of continued malarial infection. We had, as shown in Table V, 11% positive reactions as against 9% of the malarial negative cases. Our figures will put us more on guard for syphilis.

Public and private ward admissions show the same distribution in plasmodium positive as in the free cases which indicates the necessity and value of proper education, as those in higher economic brackets should at least show a lower admission rate for malaria.

*Treatment of malaria in pregnancy and puerperium.*—Williams<sup>3</sup> advises unhesitating use of quinine because its oxytoxic properties apparently are in abeyance in the presence of malarial infection, so that it can be used with impunity without fear of setting up uterine contractions. Manson-Bahr<sup>8</sup> is more cautious

and recommends care in giving quinine because, "Undoubtedly, if administered in large doses, it may sometimes cause miscarriage". He advises that quinine should be given in the minimum dose likely to be effective, say 3 grains q.8h. for 2 days. Acton<sup>16</sup> concluded from his pharmacological studies that miscarriage can only be brought about by doses of quinine sufficiently large to poison the patient.

In the puerperal state sufficiently large doses can safely be given as according to Standers<sup>3</sup> the drug exerts no appreciable influence upon the mammary secretion or the well-being of the child. On the other hand Greenhill<sup>17</sup> has a different opinion; he believes:

"Quinine may injure the baby; frequently the liquor amnii is stained with meconium; in a few instances babies have been born dead presumably as a result of the action of quinine, and in some instances deafness caused by injury of the auditory nerve can be traced to the use of quinine in labour."

Apparently this aspect of quinine therapy requires further investigation and experimentation. Quinine is excreted in the milk of nursing women. Manson-Bahr<sup>8</sup> makes the suggestion to give a few 5 grain doses of quinine during labour or soon after in order to prevent a latent infection to become active. Labour seems to have the same effect as any other shock or strain in precipitating a recurrence.

The comparatively recently developed atabrine is well borne by pregnant women in relatively large doses and is replacing quinine, especially in the treatment of pregnant cases. As for the comparative value of the two drugs Titus<sup>5</sup> states atabrine is more prompt and effective. Many of the doctors in South China believe quinine acts faster. Mackie, Hunter and Worth<sup>1</sup> state atabrine and quinine are approximately equally effective in the treatment of acute clinical malaria. The plasma concentration determines the efficiency of action. With the usual plan of dosage an effective plasma level is attained more rapidly with quinine than with atabrine.

We treated 30 cases with quinine and 20 with atabrine; 50% of atabrine treated cases were controlled after one febrile attack, while only 22% of those treated by quinine were controlled after the first febrile attack. But we do not believe the number is sufficiently large to warrant conclusion in this respect.

We experienced no untoward effect from either of the 2 drugs. The new synthetic drug

TABLE VIII.  
SHOWING COMPARATIVE EFFECT OF QUININE  
AND ATABRINE

<i>Plasmodium positive</i>	No.	%
Total admission .....	59	
Quinine after one febrile attack .....	13	22
Checked after more attacks .....	26	44
Atabrine after one attack .....	10	16.9
Checked after more attacks .....	10	16.9

paludrine will probable replace atabrine in the near future.

#### SUMMARY

1. A statistical study on the effect of malaria on pregnancy is presented on the basis of 360 admissions to the Obstetrical Ward of the Kweilin Provincial Hospital.

2. There were 59 plasmodium positive cases which represented 17% of the total admission; and another 48% had a definite malarial past history.

3. Forty-eight per cent of the plasmodium positive cases showed complications as against 18% of the malaria free cases.

4. Complications occurred in the form of abortions (16%), premature labours (32%), and stillbirths (13.5%).

5. Contrary to previous reports malaria does not seem to be a serious predisposing factor to toxæmias.

6. Falciparum infections occurred in 33 cases (55.7%) and vivax in 26 cases (44.3%).

7. Falciparum and vivax infections appeared to have the same percentage of total complications, but falciparum caused more premature labours and more stillbirths.

8. A suggestion is put forward to investigate suppressive malarial medication in cases of known malarial past history in order to prevent recurrences during pregnancy, labour and puerperium.

9. Comparative therapeutic effect of quinine and atabrine discussed.

10. The author emphasizes the importance and frequency of complications due to malaria.

The author owes a great debt to the Staff Members of the Obstetrical Department and especially to Miss Daisy Lee, interpreter; without their assistance this study could not have been made.

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### RÉSUMÉ

Etude étiologique des effets de la malaria sur la grossesse, basée sur 360 cas. Il se trouva 59 malades porteuses de plasmodium ou 17% du total des cas admis; dans un autre groupe de 48% on relevait dans le passé une histoire de malaria. 48% des cas porteurs de plasmodium eurent des complications par rapport aux 18% qui n'avaient pas eu la malaria. Ces complications furent l'avortement (16%), le travail prématuré (32%) et la naissance d'enfants morts (13.5%). Il ne semble pas que la malaria prédispose aux toxémies. On releva le falciparum dans 33 cas (55.7%) et le vivax chez 26 (44.3%). L'un et l'autre se partagèrent également le total des complications, mais le falciparum détermina plus souvent le travail prématuré et la naissance d'enfants morts. On devrait faire enquête sur le nombre de celles qui ont cessé la médication antimalarique afin de prévenir les rechutes au cours de la grossesse, de l'accouchement et des suites de couches. La quinine et l'atabrine ont des effets à peu près comparables.

JEAN SAUCIER

### X-RAY IN RUPTURE OF THE UTERUS

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WE are presenting this case, not only because rupture of the uterus is relatively uncommon, but also because x-ray played an important rôle in the diagnosis of the condition. We have been unable to find any reference in which x-ray was used as a diagnostic means for this complication of pregnancy.

The incidence of rupture of the uterus is reported by Lynch<sup>1</sup> as 1 in 1,118 labours; Sheldon<sup>2</sup> as 1 in 1,829 labours; Stander<sup>3</sup> as 1 in 1,908 labours; and Bill *et al.*<sup>4</sup> as 1 in 2,756 labours. Rupture of the uterus may occur during pregnancy or during labour and in the last report mentioned 38% of the ruptures occurred during pregnancy, all of which were close to term.

Rupture of the uterus is classified as complete or incomplete. In the former, the tear involves the mucosa, the muscular uterine wall and the peritoneum covering the uterus, while in the latter, only the mucosa and the muscle of the uterus are involved. In the complete rupture the baby and the placenta are often found in the peritoneal cavity. In the incomplete, the tear usually occurs in that part of the uterus covered by the leaves of the broad ligament and the baby remains in the uterus. Eighty-six per cent of the Delfs and Eastman<sup>5</sup> series were of the complete type.

Except where the rupture is in a Cæsarean section scar, the site of the tear is usually in the lower uterine segment. This is what one would expect in cases of excessive retraction of the upper uterine segment with extreme thinning and lengthening of the lower segment, with the tear occurring at the point of least resistance.

### ETIOLOGY

#### Cæsarean section and myomectomy scars.—

In a review of the literature one finds that a very definite predisposing cause of rupture is an operative scar in the uterus. The most common scar found is that of previous Cæsarean section, but myomectomies contribute a few (Hurd<sup>6</sup>). In the case of the latter, the scar is weakest when the myoma involves the entire thickness of the muscularis. In spite of the fact that it is often difficult to find any scar in the uterus after a Cæsarean section, Schwartz *et al.*<sup>7</sup> have demonstrated the proliferation of fibroblasts and the formation of connective tissue after a section which is weaker than normal uterine muscle. Krukenberg<sup>8</sup> in 1886 stated that 50% of pregnant uteri, which had been sectioned previously, ruptured. Delfs and Eastman<sup>5</sup> in 1944 reported that in patients who had had previous classical Cæsarean sections and in whom there was no disproportion, the likelihood of rupture of the old scar, either in pregnancy or labour, would seem to be 2%. They suggest 1% during pregnancy and 1% during labour. In their papers, based on 53 cases of rupture, a history of previous Cæsarean section was given in 20%. Bill *et al.*<sup>4</sup> report that previous Cæsarean section played a part in 56%. According to the available literature it appears that rupture of the lower uterine segment scar is very infrequent. Gepfert<sup>9</sup> reviewed the literature in 1939 and stated that



the chance of a low segment scar rupturing in a future pregnancy is only one-sixteenth as great as that of a classical section. Some of the reported cases of rupture after a low segment Cæsarean section have really been rupture of a scar which was partially in the upper segment. James<sup>10</sup> reports such a case. If a longitudinal incision is used on a patient who has not been in labour it may be difficult to limit the incision to the lower uterine segment.

**Multiparity.**—Multiparity is an important cause of rupture. Sheldon<sup>2</sup> in his report of 26 cases of rupture had only 2 primiparas and the average parity for the group was 5. Other authors offer comparable findings.

**Size of the baby.**—A large baby can be an important factor in the causation of rupture, especially if combined with multiparity and a minor contraction of the pelvis. In the Delfs and Eastman<sup>5</sup> report the average size of the baby was 3,945 gm., which is well above average. In the Whitacre and Fang<sup>11</sup> report of 44 cases, only 3 weighed more than 4,000 gm.

**Oxytocics.**—If before the birth of the baby one administers oxytocics, no matter how small the dosage, uterine rupture may be the result. Eastman<sup>12</sup> reports a case of rupture in which a total of 15 minims of pituitrin was given, with no single dose being more than 2 minims, and injections were no less than 30 minutes apart. Four per cent of the Bill *et al.*<sup>4</sup> series were attributed to oxytocics but we feel it is more important than this would indicate.

**Trauma.**—Internal version, forceps manipulation, and embryotomy still contribute a few ruptures but the number is becoming smaller every year. A blow on the abdomen as would occur in an automobile accident has been known to rupture the uterus. Predisposing causes include prolonged labour, overdistension of the uterus, malpresentations and malpositions, twins, hydrocephalus, pelvic contraction, and tumours.

**Symptoms of rupture.**—According to Beacham and Varino<sup>13</sup> impending rupture may occur without signs or symptoms but usually there is lack of progress in spite of strong uterine contractions which may be exceptionally painful and almost continuous. On examination, one finds the lower uterine segment tender and Bandl's ring may be found. The reaction to actual rupture may be insignificant or so severe as to produce shock and sudden death. Eastman<sup>14</sup> claims that shock is to be

expected in only one-half of the non-Cæsarean ruptures, and less often in others. If the rupture is of the complete type, occurring during labour, the patient suffers a sharp tearing pain and if the baby is extruded into the peritoneal cavity all uterine contractions cease. The patient goes into shock with the appearance of a fast weak pulse, fall in blood pressure, pallor, cold sweat, and air hunger.

Lower uterine segment tears usually do not bleed as much as upper segment ones. The accumulation of blood beneath the diaphragm gives pain in the shoulder, while bleeding into the broad ligament may give pain in the leg. The accumulation of blood in the abdominal cavity gives rise to pain, tenderness and rigidity, and Cullen's sign may be evident. Fluid in the peritoneal cavity may make itself apparent as shifting dullness in the flanks. Abdominal palpation may reveal fetal parts which are usually easy to discern. There is usually a change in the fetal heart, and in most cases it disappears. The uterus may be felt as a globular mass to one side of the baby and the presenting part may rise into the abdomen. Bleeding *per vaginam* may occur but is not in proportion to the amount of shock. In complete tears the intestines may pass through the rent into the uterus and vagina.

**Prognosis.**—Sheldon<sup>2</sup> reports a maternal mortality of 42.3% and an infant mortality of 82%, which is fairly representative of the literature. Rupture of a Cæsarean section scar appears to be less serious than rupture of an unsectioned uterus. The direct cause of death in the Gordon and Rosenthal<sup>15</sup> report of 30 maternal deaths as a result of rupture of the uterus, was hæmorrhage, 66%; peritonitis, 20%; bronchopneumonia, 10%; and anuria, 3%. This represented 5.4% of the total maternal mortality in Brooklyn and was equal to the mortality from ruptured ectopic pregnancy. It is interesting to note that 11 of the cases went to autopsy undiagnosed.

#### TREATMENT

Women who have had a previous operation on the uterus should be within easy reach of adequate surgical help during pregnancy and labour. One should try to carry out low segment Cæsarean sections instead of the classical type. The use of pituitrin before delivery and traumatic manipulations should be avoided.

When one recognizes a case of threatened rupture, the immediate need is to halt uterine contractions, which can be done with morphine or rectal paraldehyde. The patient is then delivered as quickly and as safely as possible. Low segment Cæsarean section is the method of choice, unless there is a possibility of infection, in which case a Porro or extraperitoneal Cæsarean section is done. If hydrocephalus is present, then a craniotomy is performed and delivery *per vaginam* carried out.

When actual rupture is diagnosed, the shock is brought under control as well as possible with blood and plasma, at which time the abdomen is sectioned, the baby delivered, and a supracervical hysterectomy done. A few uteri have been sutured.

#### CASE REPORT

Mrs. C.L., white, aged 40, para 6, gravid 7. This patient was admitted to the Kingston General Hospital on April 9, 1947, with the history that she began labour at 8.00 a.m. on the previous day. Her contractions were strong and regular and continued until 6.00 a.m. on the day of admission, when she experienced a sudden, severe pain in the abdomen after which she had complete relief. Following this, she began to suffer from generalized abdominal pain and her blood pressure fell from 160/120 to 120/100. Her doctor had not administered an oxytocic.

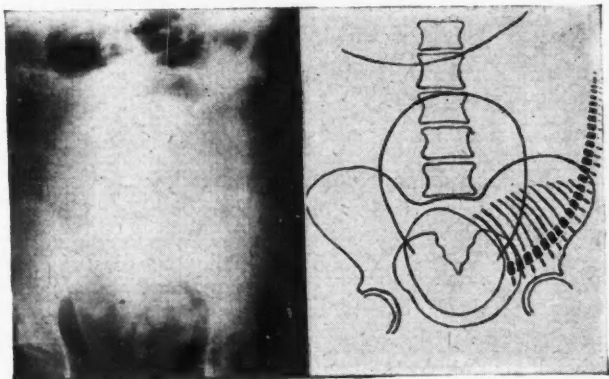


Fig. 1

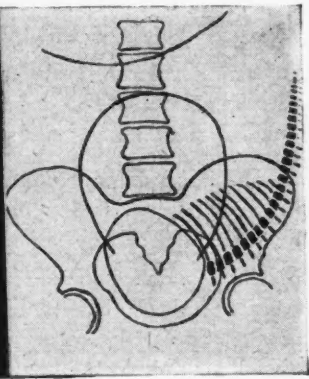


Fig. 2

At 5.15 p.m. she was admitted to hospital complaining of generalized abdominal pain and pain in the left shoulder. On examination, she appeared to be in shock. She was very pale with a slight malar flush and her lips and finger nails were cyanosed. Respirations were rapid and her breathing was mainly costal in type. On examining the abdomen no definite outline of the uterus could be felt. The baby was easily felt lying on the left side with a rounded tumour-like mass low in the abdomen on the right. There was generalized abdominal tenderness. On rectal examination the presenting part, which, according to her doctor, was visible at the vulva on the day previous, was high in the pelvis. No fetal heart could be heard. Blood pressure 120/100, temperature 99.2° F., pulse 120, respirations 25; white blood cells 11,000, red blood cells 4,230,000, Hgb. 75% (after 1,100 c.c. of blood).

We felt that we were dealing with a case of uterine rupture and had a soft tissue plate taken of the abdomen, the report of which was as follows: (see Figs. 1

and 2). A fetus is seen with the head as the presenting part. The shadow of the uterus is seen reaching as high as the level of the interspace between L.1 and L.2. The head and part of the spine and the arms are overshadowed by the uterus, but the major portion of the spine and legs are seen to be lying outside the uterine silhouette. The film presents the appearance of a rupture of the uterus with a good part of the fetus lying outside the body of the uterus.

A laparotomy was performed at 9.00 p.m., which was 15 hours after the rupture occurred. A large amount of blood was found in the peritoneal cavity. A 9 lb. dead baby was found lying on the left side of the abdomen, with the uterus, still retaining the placenta, contracted down on the right. There was a 5-inch tear in the lower uterine segment in the region of the left broad ligament. A supracervical hysterectomy was carried out. After the operation the patient developed a low grade pelvic cellulitis, which was controlled with penicillin, sulfathiazole, and blood transfusion. She was discharged from hospital May 3.

In this patient, who had no operative scar in the uterus, and no pelvic contraction, the uterus had become weakened by repeated pregnancies to the extent that it was unable to deliver a 9 lb. baby. There appears to have been little or no sign of impending rupture, which occasionally occurs as mentioned above.

It is remarkable that a patient with a 5-inch tear in the uterus could survive for 15 hours. This is explained by the fact that the baby had escaped into the abdomen, thus making it possible for the uterus to contract and so control bleeding.

As mentioned before, we can find no mention of x-ray being used in the diagnosis of rupture of the uterus, but as indicated by this case, there may be some instances where it would prove valuable. It is obvious that unless the fetus or at least part of it is outside the uterus, x-ray would be of little use. There probably are cases in which the extra handling necessary to take the plate would not be worth the risk to the patient. In view of the fact that many cases of rupture go undiagnosed, there is a definite need for additional diagnostic aids and we feel that soft tissue x-ray is one of them.

#### SUMMARY

1. A review of the literature on rupture of the uterus is given.
2. A case of rupture is presented.
3. The possibility of using soft tissue x-ray in the diagnosis of this condition is suggested.

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### RÉSUMÉ

Présentation d'un cas de rupture utérine. Revue des variétés de rupture, des causes prédisposantes et des thérapeutiques conseillées. Utilisation,—pour la première fois,—des rayons X pour confirmer le diagnostic; détails d'interprétation de telles radiographies. Compte-rendu détaillé du cas et considérations pratiques à propos de la conduite à tenir en présence de ruptures imminentes et confirmées.

JEAN SAUCIER

## THE OPERATION FOR CLOSURE OF PATENT DUCTUS ARTERIOSUS

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THIS comment on the surgery of patent ductus arteriosus would be incomplete without mention of Maude Abbott's<sup>1</sup> contribution to the morbid anatomy of the condition, the courageous approach and successful ligation by Gross<sup>2</sup> in 1938, and the direct attack on subacute bacterial endarteritis by Touroff<sup>3</sup> in 1940.

The ductus arteriosus serving the fetus by shunting the blood from the pulmonary artery to the aorta, closes spontaneously at birth and only very occasionally remains patent. If patency persists (as it does probably in about 0.1% of persons)<sup>4</sup> the flow of blood is from the aorta to the pulmonary artery because of the obvious difference in the two pressures. This flow is dependent upon the calibre of the ductus and has been estimated as 45 to 75% of the systemic flow.<sup>5</sup> The increased load on the heart may lead to eventual failure and the diminished systemic circulation to underdevelopment. Vegetation within the ductus produced by the eddying of the stream, not infrequently results in fatal subacute bacterial endarteritis. For these reasons Abbott's 92 cases studied at autopsy averaged 24 years of age at death;<sup>1</sup> Shapiro and Keys<sup>6</sup> in another analysis state that patients alive at 17 years average 35 years at death. Bullock *et al.*<sup>7</sup> followed 80 cases and found that 14% died by the age of 14, 50% by the age of 30, and 71% by the age of 40; two patients survived to the age of 66.

It is obvious from these studies that surgical intervention is indicated in cases showing early signs of cardiac decompensation and, following the lead of Touroff, in subacute bacterial endarteritis; underdevelopment in a child may also be considered an indication. The benefit derived from ligation of the ductus for cardiac decompensation is obvious, as is the improvement in the underdeveloped child with a lessened systemic flow. The brilliant results of ligation in subacute bacterial endarteritis are rather difficult to understand unless one believes the diminished pulmonary flow allows the lung to sterilize the blood before returning it to the systemic circulation, or the intima of the ductus is embryonic in type and liable to minute thromboses. In the hands of an experienced operator such as Gross, with a mortality of less than 10%, operation may be indicated in every case in which the diagnosis is established. Contra-indication to ligation exists if the ductus is acting as a compensatory mechanism for a co-existing congenital defect such as pulmonic stenosis.

The optimum age for operation is from 5 to 10 years, before the ductus has become thinned-walled or even atheromatous and before the pulmonary artery has become permanently dilated. The operation is not difficult but is fraught with considerable danger of hæmorrhage both from the ductus itself and from the adjacent and often overlapping pulmonary artery. The technique has been fully described by various authors and usually consists of an anterior approach through the 2nd or 3rd interspace, division of the mediastinal pleura between the phrenic and vagus nerves above the lung hilus and identifying the ductus as the recurrent branch of the vagus winds about it. Dissection is carried out from the aortic side since the adventitia of the aorta continues on to the ductus and lends it strength. Isolation should progress slowly both above and below before proceeding posteriorly in order that a clamp may be applied in the event of hæmorrhage. After isolation, ligation in continuity after the method of Blalock<sup>8</sup> is the safest and most logical procedure, division and ligation as practised by Gross is an ideal, and in that surgeon's hands, a safe procedure. The thrill which is easily felt at the junction of the ductus with the pulmonary artery should disappear following ligation. The steps in the ligation after the manner of Blalock are illustrated by



the accompanying diagrams. The mediastinal pleura is closed and lung inflated as the chest wall is closed. Postoperatively penicillin is administered and oxygen given if necessary. Convalescence should be rapid and uneventful.

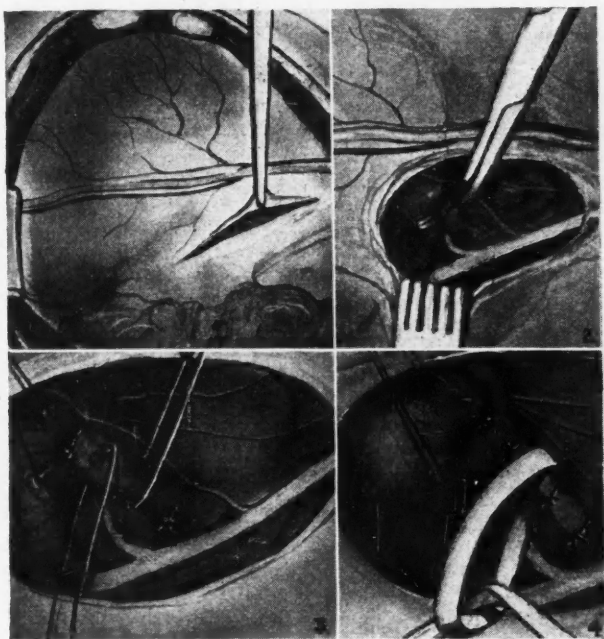


Fig. 1.—The incision in the mediastinal pleura between the phrenic and vagus nerves. Fig. 2.—The ductus which is often overlapped by a large pulmonary artery, is identified by the recurrent laryngeal nerve passing medially and posteriorly. Fig. 3.—A purse-string suture of double 0 silk at each end, two transfixion sutures. Fig. 4.—Umbilical tape tied firmly. (Diagrams modified from Blalock)

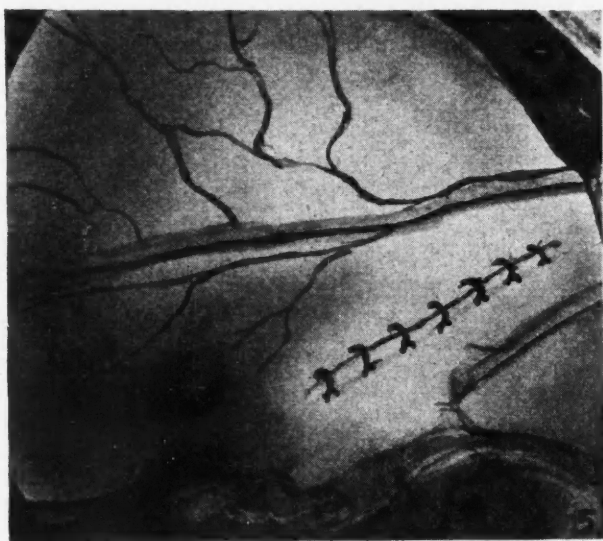


Fig. 5.—The mediastinal pleura closed. (Diagram modified from Blalock)

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#### UTERINE INERTIA\*

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"If the disasters of midwifery were traced back to primary causes, the majority of them would be ascribed to failure of the dilating and expulsive powers of the uterus. A feeble uterus cannot flex or rotate a head in occipito-posterior, nor force down a breech. How often in A.P.H. have we prayed for strong contractions, or, in watching labour in a flat pelvis, predicted adequate moulding and delivery if only contractions would become regular and strong?"

"Contrary to widely held views, the chief difficulties of labour are due to disorders of function, as opposed to mechanics. The failure of adequate uterine contractions with co-ordinated relaxation of cervix and perineum constitute the supreme difficulty in labour" (Bourne).

The physiology of labour should be discussed, but space forbids. We shall only quote Bourne "that perfectly normal labour is largely a matter of local myogenic contractions and local reflex activity of the uterus itself; the sympathetic inhibits contractions of human uterus in labour; and external stimuli, whether emotion or other reflexes, are able to modify this activity".

#### FACTORS AFFECTING UTERINE CONTRACTIONS

##### *Uterine muscle and its intrinsic nerve control.*

—Fibroids; previous inflammatory disease with adhesions; aged primiparity; myasthenia gravis; poor development from hereditary, hormonal or nutritional causes.

*Mechanical factors.*—Normality is encouraged by: (a) smooth, well-fitting presenting part in lower uterine segment; (b) normal degree of uterine distension. It is impeded by (a) going to bed too early; (b) abnormal adhesions of membranes to lower segment; (c) poorly fitting or rough presentations and pendulous abdomen; (d) full bladder or rectum; (e) obstruction to delivery may cause cessation of contractions, especially in primiparæ. (The opposite may occur, especially in multiparæ). Reflex action by impulses generated by uniform pressure of head on cervix, vagina or perineum seems to

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encourage normal contractions. The lack of such impulses in obstruction may result in inertia.

*Psychic factors.*—Tremendously important. Mental attitudes, such as fear or apprehension may affect labour. It is probably largely due to the psychic element (which is almost entirely inhibitory or inco-ordinating in its action) that labour in civilized women is so much more of an ordeal than in primitive races.

*Blair-Bell stressed the importance of pressor and de-pressor substance.*—He states that calcium in optimum concentration is essential. Potassium has no effect. Magnesium is depressing. It has been thought by some that CO<sub>2</sub> concentration increased contractions. Not much evidence.

Bourne investigated many substances and concluded that: gas oxygen has no effect; quinine has little stimulating action (although it may sensitize the uterus to respond better to stimuli); morphine renders contractions less frequent but more effective; atropine stimulates. Adrenalin in labour abolishes action, while acetylcholine augments it for a short time. Investigation at Toronto of choline in cord blood showed that the average content was highest in short labours. Pituitrin is a powerful pressor substance. Progestin, and probably also A.P.L., inhibits and oestrin may stimulate. Possibly toxin is a factor in the rapid labours often occurring in severe toxæmias. Blair-Bell thought late inertia was due not to fatigue but lack of pressor substances, since it nearly always reacts to pituitrin, which it would not do if really fatigued.

In addition to the more immediate effects of hormonal deficiency or imbalance there is also the effect of long-standing imbalance. Goodall, Taylor, DeLee and others describe the type of woman most likely to have slow, tedious labours—the “dystrophica dystocia syndrome”, and tendency to sterility or aged primiparity. Irving too states that excessive gain in weight during pregnancy is often followed by inertia. Other factors of lesser importance may be weather and geographical locality.

#### CLINICAL TYPES OF UTERINE ACTION

When all these factors are present in optimum degree and perfectly balanced, we expect a rapid or even precipitate labour; with less optimum conditions, an ordinary normal labour, or a slower labour; when still less optimum, a

slow labour, or one that may come to a standstill.

But in all these, in spite of all degrees of speed or slowness, the cervix and body of uterus tend to act in sympathy with each other, and there results that co-ordinated physiological act which we call for short, dilation of the cervix.

There is another category of labour in which there are elements which distort this, and “sympathy” is relatively or completely absent.

The recognition of these two categories of labour is essential and fundamental. The terms “sympathy” and “lack of sympathy” are Wentworth Taylor’s and, while not ideal, they do express the meaning. The term “inertia” is not good, since it is used loosely to cover quite different conditions which should be clearly differentiated—both the slow but co-ordinated action and the varieties of action in which sympathy is lacking.

In the *first category*, rhythmical contractions alternate with complete relaxation. The contractions may be infrequent, feeble or of too short duration; they may intermit for hours or days, and may be difficult to distinguish from false labour. There is not much suffering. Since membranes do not rupture before the cervix is dilated (except by pure accident) there should be no maternal or fetal distress even in long labours of this type. It is true, however, that the slowness of labour may alarm the patient and, by making her frantic with fear, thus alter the whole aspect of the labour by changing it from a simple slow into an inco-ordinate one.

In the *second category* (in which there are not only full-blown manifestations but often milder forms frequently overlooked) there are two main subdivisions of inco-ordinate labour recognized by both Solomons and Taylor and by DeLee.

*Spasm of uterus or cramp pain*, marked by irregular, painful and inefficient action, chiefly in first stages, and of all degrees of severity. Onset of labour may be normal, or it may be colicky from the first. Instead of rhythmical orderly contractions with intervening complete relaxation, the uterus becomes panicky; the cervix fails to be progressively taken up and dilated; the uterus is tense and tender at all times and the fetus difficult to palpate. Contractions superimposed on this irregular spastic

condition are short, sharp and not maintained; and advance is inordinately slow compared to the effort.

Even in the mildest cases it is more painful than is well co-ordinated labour. In its severe forms it is characterized by excruciating pain in lower abdomen. Pain tends to persist even after contractions have passed off, and whenever an attempt is made to palpate the abdomen, the patient says, "Wait a minute. I am having a pain." Pain is badly borne because of the lack of normal rhythm; the patient loses patience and morale, and this nervous frenzy further disorganizes uterine action. The term "panicky" describes both the patient and her uterus. Membranes tend to rupture early, predisposing to sepsis and exhaustion, and the spasm interferes with fetal oxygenation. Altogether the condition causes danger to mother, to baby and to professional reputation.

*Tetanus or stricture of uterus or active retention of fetus.*—This is essentially a second stage complication. Many cases of delay in second stage loosely ascribed to inertia or to disproportion are in reality due to milder degrees of constriction ring, which likewise explains some cases of difficult forceps extractions. More severe cases have continuous pain and lead to fetal death.

#### TREATMENT OF UTERINE INERTIA

The first essential is diagnosis. This means more than just calling a prolonged labour inertia, or labelling it primary or secondary. These latter terms have been avoided as being indefinite. Some writers use them to mean of early or of late onset, which is a useless distinction. Solomons uses "primary" to designate inertia in which no mechanical cause is found to account for the condition (such as disproportion, hydrocephalus, malpresentation), and "secondary" if such a cause exists. This terminology would be useful if generally adopted. The recognition or elimination of such a cause is extremely important. Then having eliminated such, the distinction must be made as to which category of labour it belongs.

*Prophylaxis.*—Ante-natal care permits recognition and treatment of abnormalities, encourages a good dietetic hygiene, and the gaining of the patient's confidence.

*Treatment of cases with slow but co-ordinated action (weak pains).*—(1) With unruptured membranes there is little call to interfere except

for food, sedatives and reassurance. Titus says dextrose supports and stimulates. (2) Various methods of mechanical stimulation: A tight abdominal binder may work wonders, perhaps by pressing the head into lower uterine segment and reflexly stimulating better contractions. This also corrects pendulous abdomen. In occipito-posterior, Buist's method of pads and binder may be of further help. Except for the discomfort of a tightly applied binder, there seems to be no ill effects and the results are often dramatic. Hot water bottle to fundus; and hot packs. Walking about. Enemata—especially hot milk and molasses—may be stimulating. Keep bladder empty. Methods of directly stimulating the cervix have not a very large place because we want to preserve the membranes, and as long as they are intact, not much urgency exists. However, the following are useful:

(a) When making a vaginal examination, insert fingers through cervix and strip membranes off the lower uterine segment. Following this, the cervix may be further stimulated by separating the index and middle fingers and so gently stretching the cervix (this is not an effort to actually dilate the cervix but to stimulate).

(b) Not uncommonly, in late first stage, a thick anterior lip of cervix will be found pinched between the head and symphysis: retracting it forward and pushing it up often results in a much improved type of labour.

(c) I have not had experience with such procedures as hydrostatic bags or cervical packing, and have very rarely used hot anti-septic douches, although they may occasionally be helpful.

(d) If membranes have already ruptured, Willett's forceps with one or two pound weight-traction to increase the pressure against the cervix should stimulate contractions, and have been recommended. In my experience it has been rather disappointing.

(e) If fetus is dead, perforation and weight traction.

(f) If breech is presenting, bringing down a leg provides a good dilating wedge. But we are rarely justified in doing a version for this purpose. In early labour it is difficult to know if it is needed, and later it is out of the question.

(g) For associated disproportion or malpresentation, suitable treatment as indicated.



3. *Drugs used to stimulate labour.*—Castor oil and enemas are certainly valuable. Since many cases of sluggish labour are very like false labour, and since medical induction is usually indicated in false labour in the hope of changing it into the real thing, the use of quinine following the castor oil and enema should be worth considering in these cases. Over-dosage of quinine must be avoided—it might be dangerous to fetus—and although small doses will sensitize the uterus to stimuli, over-dosage may depress the uterus for days. (The doses usually used for induction are much too large.) Much confusion has arisen in the use of quinine due to failure to distinguish between the sluggish uterus where its use in small doses is probably both safe and useful, and the panicky uterus where its use is dangerous to baby and detrimental to mother.

*Pituitrin.*—The above statement (about quinine) is to some extent applicable to pituitrin. Although it is unquestionably safer for the practitioner to avoid its use entirely until the end of the third stage, still, in cases where there is no obstruction and where the uterine action is sluggish but co-ordinated, its use in small dose (not exceeding two units at hourly intervals) may be useful and is unlikely to cause harm if used in this type of case. Its use in inco-ordinated labour is disastrous; and it must always be regarded as a dangerous drug even at the best.

How often have we wished for some drug that would stimulate a lazy uterus and still be free of the dangers of pituitrin! True enough there is nothing else as spectacular as is pituitrin; but there are drugs worth using. Blair-Bell used to maintain that one-third of cases responded well to calcium injections. Recently I have seen reference to use of ascorbic acid in doses of 100 to 500 mgm. with rapid onset of oxytoxic action. I have not yet had any experience with it to report. Oestrogen was considered useless by Bourne, but Jeffcoate (1937) reported some success. I have used stilbœstrol by mouth in a good many cases in doses of about 10 mgm. every three hours. It seems often to increase the frequency and strength of contractions and sometimes the effect is quite marked. There are no ill effects except the inhibiting effect on lactation.

In view of the theory that sympathetic stimulation inhibits labour, acetylcholine should be worth trying although there are few refer-

ences to its use in literature. I have used carbachol in many sluggish labours, both alone and as a supplement to stilbœstrol. Again, there are no harmful effects except that an occasional patient gets pallor and excessive sweating. The results are often (although by no means always) gratifying and sometimes it is almost as dramatic as pituitrin.

With plenty of reassurance and of sedatives to prevent emotional disturbances becoming inhibitory, with the use of snug abdominal binders, and drug stimulation by stilbœstrol and carbachol, most of these slow labours can be stimulated satisfactorily, and I find excessively prolonged labours rare indeed.

Second stage delay will not here be discussed as forceps may be used when indications are clear and the conditions fulfilled. In rare cases of marked inertia, chiefly in aged primiparæ and especially if associated with mild disproportion, Cæsarean section may be indicated.

#### TREATMENT OF CASES MARKED BY INCO-ORDINATED ACTION AND DELAY

Prophylaxis includes psychotherapy, nutrition, dextrose, sedatives, and diagnosis of obstetrical abnormalities. Avoid upsetting remarks and frantic efforts to make the patient "bear down" in first stage.

When inco-ordinate action occurs either early or later in labour, plentiful use of sedatives is imperative: magnesium sulphate, heroin, barbiturates, paraldehyde, oil-ether, and chloral. If these cases are recognized early and adequately treated in this way, a great deal of suffering and worry of patient and physician alike may be avoided. If membranes have ruptured, keep in bed. Heat is relaxing: heat to the abdomen, rarely hot antiseptic douches; hot bath is an old remedy and Vignes still uses it in spite of theoretical danger of infection, adding formalin to the bath and finding no ill-effects and often a speedy delivery. DeLee and Greenhill recommend it also.

Dextrose, calcium, œstrin and atropine may be tried: Whitehouse injected atropine into the cervix, but since I saw one of his cases with resultant puerperal sepsis, I have been prejudiced against it. Adrenalin may stop action for a short time. Oxytoxics—both quinine and pituitrin—must be utterly condemned in these cases: they will aggravate and intensify the inco-ordinate action and probably kill the baby. Other stimulating treatments such as

Willetts's forceps, bags, etc., will probably do more harm than good.

In the majority of cases, especially if early and mild, the above treatment is effective, but it does not always succeed in restoring normal action. Labour then drags on with progressively increasing risk: Bourne estimates this as follows:

Maternal mortality .....	10%
Maternal sepsis .....	28%
Stillbirths .....	38%
Neo-natal deaths .....	6%

So, although patience is a most commendable virtue, it may be carried too far.

As long as membranes are intact, danger is negligible; but in protracted dry labour with spasm failing to respond to sedation, operative measures are indicated.

Although I think that a great many Cæsareans are done unnecessarily for other difficulties which should be treated by obstetric art rather than by surgery, I believe also that this is the one indication for which Cæsareans are not done often enough. This, I think, is because of the failure to recognize this most important and dangerous condition and its implications. In my opinion, a case of inco-ordinate labour which, after a reasonable trial of adequate sedation, does not respond by approaching normality and progressing favourably, should be treated by section without necessarily waiting for maternal and fetal distress.

Labour may have been long with many vaginal examinations and risk of infection. If the os is less than half dilated and the baby alive, even here I think lower segment section is the treatment of choice. The alternative is delivery from below, and this presents great problems. The usual suggestions have to do with incisions of cervix. Bourne's summary of the situation is this:

"There comes a time in labour of this sort when good obstetrical judgment realizes that sedatives and patience will accomplish little more and mother and baby will deteriorate. Then explore the dilatability of the os under anaesthesia. If soft and dilatable, open it gently and push it up over the head after applying forceps. The greatest difficulty and danger is if the os is not dilatable. If mother and baby are good and ordinary possibility of infection ruled out, lower segment Cæsarean is safest. If first seen at a later date with baby dead and mother in urgent need, manually dilate, perforate and if necessary use weight traction".

Wentworth Taylor (Birmingham) in a personal communication recommended an extremely

useful measure to be used in these trying cases. I hesitate to mention it lest it be abused and used unnecessarily, since it is really a last resort measure to escape from a desperate situation. I have used it in a few such cases with completely satisfactory results.

The procedure is to give a deep general anaesthetic and then to inject 2% novocaine (about 10 c.c.) in each of four quadrants around the cervix. Then, *wait five minutes by the clock* (this is important; an estimate of time will inevitably mean allowing an insufficient length of time to elapse) and after this five minute interval insert the hand. The cervix, vagina and perineum will dilate widely and the uterus relaxes, so that forceps may be applied and the cervix pushed up over the head and delivery effected. This procedure is for cases with cervix already about three-quarters dilated—not for tight closed cervix.

Again I would emphasize that this procedure is not one to be employed lightly or without adequate justification; but where circumstances demand it, it is preferable to incisions of cervix or manual dilatation by other means.

#### SUMMARY

1. The term "uterine inertia" is often used loosely for any case of slow labour.

2. It is important to differentiate two categories of slow labour: (a) the sluggish uterus with slow but co-ordinate action; (b) and the colicky or frantic uterus with inco-ordinate action.

3. In the first, patience, supportive and various stimulating measures may be employed. In the second, stimulation is dangerous and useless: the foundation of treatment is adequate sedation; if this fails, Cæsarean section should be employed before distress occurs. Alternative methods are also considered.

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The common denominator of success—the secret of success for every man, who has ever been successful—lies in the fact that he formed the habit of doing things that failures do not have to do.



## ANÆSTHESIA FOR CHEST SURGERY

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THE advances made in thoracic surgery in recent years have added greatly to the burden of responsibility upon the anæsthetist, for in no other type of surgery is the eventual result so dependent upon the anæsthetic management. Surgical techniques for the trans-thoracic approach of the vagus nerve and sympathetic ganglia have become popular, lobectomies and pneumonectomies have become relatively commonplace, and cardiac surgery for the removal of foreign bodies, for the correction of congenital lesions, and for the relief of constrictive pericarditis, is being done in the larger centres. The amount of surgery in sanatoria for the treatment of the tuberculous patient has much increased.

Reports from the various centres indicate that all agents and techniques are used. It has been stated that the agent is of secondary importance to the requisite that the procedure be safe, and contribute to rapid, uncomplicated recovery without compromising sequelæ.<sup>1</sup> The choice of anæsthetic agent and technique should be made after carefully considering the patient from the standpoint of disease and general condition, the surgery to be done, and the complicating difficulties which may be anticipated. Very often, patients requiring thoracic surgery are poor risks from the anæsthetic standpoint. Often they have been the victims of a protracted illness and have spent long periods in bed. They will often have accompanying secondary anæmia and nutritional disturbances.

The position of the patient on the operating table, in which the healthy, functioning, good lung occupies a dependent position, hinders respiratory exchange. This is decreased further because the weight of the body limits rib movements and the weight of the viscera against the dependent diaphragm reduces diaphragmatic action. Respiratory exchange is hindered further if an intrapleural procedure is undertaken with an open pneumothorax.

Of the complicating difficulties, probably the most troublesome is the control of mucus and pathological secretions in the tracheo-bronchial tree. In infected cases, adequate removal of any infected secretions while the patient is under anæsthetic and until he has regained his cough reflex, is of the most importance in pre-

venting spread of infection to the good lung. In most thoracic operations, there is more than average bleeding. This is consistently so with thoracoplasties. Reflex effects are prone to occur: of these we mention the bronchospasm and intercostal muscle rigidity, which often occurs following the passing of an endotracheal tube, and the cardio-circulatory reflexes which are prone to occur during thoracic surgery.

A large part of our work in thoracic cases has been with tuberculous patients. In this group of patients, the preoperative evaluation and preparation is most important. Some cases will require preoperative blood and amino-acid therapy. The estimation of the efficiency of the ventilating mechanism has become necessary information in evaluating the patient's fitness for the operation. Many tuberculous patients that are considered for major thoracic surgery, such as lobectomy or pneumonectomy, have had respiratory disease for years, and may have, as a result of their respiratory deficiency, minor degrees of chronic anoxæmia. An estimation of respiratory function in these patients will give an evaluation of whether sufficient respiratory function will be left following the operation. Although no single test has been devised that will give a comprehensive picture of respiratory function, the combination of tests possible with the spirometer and the broncho-spirometer allow an interpretation of respiratory function that is a comparatively correct estimation of the patient's ventilating mechanism.<sup>2</sup> Postural drainage should be used in patients with large amounts of sputum. This type of patient should have at least a few hours during the morning of operation to clear secretions from his respiratory tract. Preferably they should be operated on in the afternoon. In some cases, it may be considered advisable to carry out bronchoscopic aspiration of secretions previous to operation.

### SEDATION

Preoperative sedation should not be excessive, and should be withheld as late as possible so that a dulled cough reflex will not occur to promote accumulation of secretions. In practice, we have ordered sedation  $\frac{3}{4}$  to 1 hour preoperatively. Some centres advocate giving sedation intravenously on the patient's arrival in the operating room, in which case, at least 5 minutes should be allowed to elapse before starting anæsthesia.<sup>3</sup> The advantages of induc-



ing anæsthesia with sodium pentothal has, in my opinion, outweighed the disadvantages. Tuberculous patients who are in hospital for long periods, and particularly thoracoplasties who undergo repeat operations, talk among themselves, and by so doing enhance the fears of those who are to undergo operation. It has been my experience that under cyclopropane induction many become excited, and the resulting stimulation disturbed the early anæsthetic period. Since I have been using pentothal for induction, this difficulty has disappeared almost completely.

#### INTUBATION

It has been our practice to intubate all patients, usually by the oral route. Should blind intubation be deemed advisable or necessary, pentothal should not be used as an induction agent. The combination of pentothal with cyclopropane increases vagal tone, and the tendency to laryngospasm, and makes blind intubation more difficult. The use of nupercainal (1% nupercaine ointment-Ciba), smeared on the distal end of the endotracheal tube has produced sufficient anæsthesia to prevent undesirable reflexes, and to allow a light plane of anæsthesia in suitable cases. The problem of reflex disturbances, following the stimulation from intubation, is a very real one. In patients in whom the control of secretions is difficult, or in whom the spread of infection is feared, a period of "bucking",<sup>1,3</sup> may cause considerable concern to the anæsthetist. The term "bucking" is a descriptive term applied to the exaggerated coughing effort which occurs when an endotracheal tube prevents closure of the glottis. This phenomenon is most commonly seen following the stimulation of passing an endotracheal tube under light anæsthesia. Individual susceptibility varies greatly, so much so that some individuals are spoken of as "broncho-sensitive" when they show a particularly high tendency to coughing spasms, with associated bronchial spasm and intercostal muscle rigidity. In such individuals, these bouts are prone to recur during operation whenever mechanical stimulation is produced by surgical means. Surgical stimulation is particularly prone to occur from manipulations of the pericardium, about the hilus of the lung, or over the diaphragm.

In practice, "bucking" is seen most often when agents are being used which tend to sensitize the vagal mechanism and produce

high vagal tone. When vagotonic drugs are being used, it is desirable to spray the larynx and upper portion of the trachea with suitable topical anæsthetic solution before intubating. We do not believe that the use of an inflatable cuff on the endotracheal tube is necessary. Pressure of the cuff on the trachea will often cause undesirable reflexes unless the anæsthesia is maintained at a relatively deep level, and it seems likely that the mucosa or its delicate ciliary apparatus may be damaged. We have used a pharyngeal pack of fine mesh gauze impregnated with paraffin oil or vaseline, or have used a short tube lying free under a small, close-fitting, face mask. In regard to intrabronchial tubes,<sup>4</sup> their use is technically difficult, and has several associated hazards. The proper placing of these tubes is difficult and trauma may be occasioned. They are prone to come out of place at inopportune times, even when inserted by those who are skilled in their use. When they are in place, they dam back secretions and pus contained in the operative area, and if they become dislodged the good lung becomes flooded suddenly with this material. They are unsatisfactory if a pneumonectomy was planned and it is found later that a lobectomy is sufficient, for the other lobes on the blocked side will be seriously contaminated. For similar reasons we do not advocate bronchial tamponage. Aspiration of tracheal secretions should be carried out whenever indicated. In thoracic operations, thorough aspiration should be done as the chest wall is being opened, or after manipulation or expansion of the collapsed lung. At the end of the operation, a thorough tracheo-bronchial toilet should be carried out by aspirating with a urethral catheter through the endotracheal tube. Before the tube is extubated, the mouth and pharynx should be aspirated for accumulated secretions.

#### INTRA-THORACIC SURGERY

For the tuberculous patient, the anæsthetic of choice, in our opinion, is cyclopropane. For intrathoracic surgery, we have used cyclopropane alone with the closed carbon dioxide technique using a circle filter. We have started compensated respiration early by applying rhythmic, intermittent, manual pressure in time with the normal respirations. The term compensated respiration implies the assistance to normal, spontaneous, respirations by applying manual pressure (6 to 12 cm. water),

on the breathing bag during the inspiratory phase, and removal of the pressure on the expiratory phase. During the operation, the amount of manual pressure necessary to ventilate the dependent lung, to prevent paradoxical breathing, or mediastinal flutter without causing the lung to expand into the operative area, is judged by direct vision. The incidence of paradoxical respiration and mediastinal instability is greatly reduced when compensated respiration is applied. Its application allows free ingress and outflow of anæsthetic gases and prevents the occurrence of pulmonary decompensation. Pulmonary decompensation has been described as that condition in which respirations become rapid, jerky, and the mediastinum flaps back and forth with each respiration.<sup>1</sup> It is thought to be caused by inadequate oxygenation and carbon dioxide retention, and tends to become progressively worse. It makes surgical manipulation extremely difficult.

From the point of view of maintaining circulatory efficiency, whole blood and plasma should be readily available and used freely. In operations involving the heart and great vessels in which serious cardiac dysfunction might possibly occur, the use of dilute procaine intravenously during the operation seems to be indicated,<sup>5</sup> and should be started early and maintained throughout. It may be desirable, in these cases, to reduce vagal tone by local application of procaine to the pericardium or local infiltration about the hilus. In those cases in which control of tracheo-bronchial secretions is difficult, or in which it is difficult to maintain a good colour even with high concentrations of oxygen, we believe bronchoscopic aspiration should be done at the end of the operation. In these cases, removal of a bronchial plug or a collection of secretion will often be possible. In cases in which bronchoscopic aspiration is not required, it is desirable to have the patient as light as possible at the end of the operation, so that the reflexes will be active immediately in controlling secretions. Thorough tracheal toilet should be carried out with a urethral catheter through the endotracheal tube. Stimulation by the catheter will provoke bouts of coughing, thus aiding in clearing the tracheo-bronchial tree.

It has often been stated that the incidence of spread of disease in tuberculous patients is high following major thoracic surgery. Often the spread, as seen by x-ray, will appear a few days

postoperatively, and will apparently clear completely within a week or two. These cases we believe are, sometimes at least, due to an area of atelectasis, which is followed by collection of secretions in the smaller bronchioles, becoming visible by x-ray. Since secretions are not absorbed from the bronchioles, it is understandable that x-ray signs will be visible for some time, once secretions have collected.

#### EXTRA-THORACIC SURGERY

Thoracoplasties do not present as many difficulties as do the intra-thoracic operations. As has been discussed already, the position of the patient hinders respiratory exchanges. Braces and retractors must be arranged to cause as little interference with diaphragmatic and thoracic movements as possible. Frequently, there will be a pneumothorax present on the side of the "good" lung. The sum total evaluation of the patient's respiratory function will almost always reveal an impaired ventilating mechanism, with a varying amount of non-functioning lung tissue. Often these patients will demonstrate a minor degree of chronic anoxæmia. During operation, they are placed in a position which hinders respiratory exchange and are then given an anæsthetic, which depresses respiration. Adequate oxygen supply can be maintained by increasing the oxygen in the respired atmosphere, but we do not believe that satisfactory elimination of waste products such as carbon dioxide is possible under such circumstances. For this reason, we believe that these patients should be maintained at as light a level as possible to afford maximum respiratory exchange, and if for any reason respirations are too "depressed", assistance should be supplied by instituting compensated respiration.

We believe that the use of the endotracheal tube is necessary in thoracoplasties, firstly in the event of a pleural tear to better control respiratory exchange, secondly in the event that compensated respirations are deemed necessary throughout the operation, and thirdly to aid in preventing laryngospasm and respiratory obstruction occasioned by light anæsthesia. It has seemed to us that in such cases a combination of synergistic drugs with cyclopropane has proved more satisfactory than cyclopropane alone. We have used pentothal in this combination most frequently. The most satisfactory technique has seemed to be continuous



drip pentothal, using a solution of 1/1,000 pentothal (1 gm. per litre), with light cyclopropane. The average dose of pentothal for induction and maintenance which I have used, has been  $\frac{1}{2}$  to  $\frac{3}{4}$  gram per case. Probably the use of pentothal-curare with light cyclopropane, nitrous oxide, or ethylene, will prove to be very satisfactory. We have not noticed, in using these techniques, any increase in surgical shock during operation. Patients regain their full reflexes very quickly, and do not demonstrate any tendency to postoperative depression.

#### HEMORRHAGE

The problem of bleeding during thoracic operations is a very important one to the anæsthetist. It is therefore obvious that the free use of blood in replacing blood loss is imperative, not only to prevent serious shock, but also to keep the patient's vitality at a sufficiently high level to ward off infection and to allow normal healing to occur. There is a very marked difference between patients with regard to the tendency to bleed. We have observed that those patients who develop an elevation of blood pressure above their normal level during operation have a greater tendency to oozing, and consistently, these patients will show a still greater tendency to elevation of blood pressure and to oozing with each stage of thoracoplasty. It has seemed to us that this tendency exactly parallels the decrease in respiratory capacity and the increase in non-functioning lung tissue to which the patient is subjected. We believe that the cause is an impairment of the elimination of carbon dioxide, due to impaired respiratory function.<sup>6</sup> The use of pentothal-cyclopropane combinations, along with anæsthesia at as light a plane as possible, has reduced this tendency, according to our observations. In some centres, electrocautery is used to control bleeders, and should decrease the amount of bleeding and save valuable time. Heretofore, there has not been a satisfactory inhalation technique of anæsthesia that was non-explosive. Perhaps pentothal-curare-nitrous oxide will fill this requirement.

#### INTRAVENOUS NOVOCAINE

The recent work being done with intravenous novocaine in combination with other anæsthetic agents shows promise that this drug will become a very valuable drug available to the

anæsthetist. The value of intravenous novocaine in controlling cardiac arrhythmia occurring in the anæsthetized patient has been used with success by Burstein and Alexander.<sup>1</sup> That it in addition seems to exert a stabilizing effect on a combined anæsthetic in reducing surgical stimulation and reflex effects, is suggested by those with experience in its use.<sup>7</sup> The combination of pentothal-intravenous novocaine and cyclopropane shows evidence of synergism. Smaller amounts of pentothal and cyclopropane are required to obtain a satisfactory level of anæsthesia to afford adequate analgesia, and to eliminate surgical stimulation. This combination of synergistic drugs causes less depression of respiratory exchange. In some cases, the relief of postoperative pain is most impressive, and this effect is becoming more sure with more adequate procaine therapy. The use of intravenous novocaine in thoracic patients seems to us to be indicated. Firstly, because under cyclopropane anæsthesia cardiac arrhythmias are prone to occur;<sup>5</sup> secondly, because cyclopropane, due to its marked respiratory depression, should not be maintained at a deep level,<sup>6</sup> and surgical stimulation and reflex effects are liable to occur with light cyclopropane; thirdly, to allow postoperative relief of pain, allowing postoperative sedation to be decreased to a minimum with a resulting more active cough reflex in handling mucus and tracheo-bronchial secretions.

#### SUMMARY

We have discussed our methods of general anæsthesia as used for thoracic surgery of tuberculous patients. We have found their application for thoracic surgery in non-tuberculous patients equally satisfactory. There has been no mention of other types of general anæsthesia, or of local, spinal, and regional anæsthetic procedures. This omission has been because we have been endeavouring to present the methods which we have been using, and not because of lack of appreciation of the value and good results which have been obtained with their use by others.

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## INTRAVENOUS PROCAINE\*

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THE intravenous administration of procaine was first advocated in 1908 by Bier<sup>1</sup> to produce anaesthesia in the extremities; Goyanes<sup>1</sup> of Spain in 1908, also obtained analgesia by the inter-arterial use of local anaesthetic agents. Adequate anaesthesia for surgical procedure was established by both these men but the inaccessibility of arteries was the disadvantage of Goyanes' technique. A modification of the original intravenous technique of Bier is being utilized today by Herreros<sup>2</sup> of Mexico, under conditions far from favourable, with gratifying results.

Until 1940, with these three exceptions, the intravenous administration of procaine has been accidental, in the course of a local infiltration or attempted spinal anaesthesia, precipitating extreme anxiety for the patients' welfare and unfortunately, on occasion, medico-legal investigation.

In September, 1940, Lundy,<sup>3</sup> relieved the pruritus of jaundice by 1/1,000 procaine intravenously. Rovenstine and Burnstein,<sup>4</sup> in 1940, reported laboratory studies of the prophylactic and therapeutic treatment of ventricular fibrillation with intravenous procaine during cyclopropane anaesthesia. Barber and Madden,<sup>5</sup> in 1944 used 2% procaine intravenously to lessen the occurrence of ventricular fibrillation in anaesthesia; Gordon,<sup>6</sup> reported in 1943 his original work with procaine 1/1,000 intravenously to procure analgesia in burns. Webster,<sup>8</sup> in 1945, reported the intravenous use of procaine for the relief of postoperative pain. Burnstein,<sup>7</sup> in March, 1946, related his experience using 1% procaine intravenously for the cardiac arrhythmias occurring in chest surgery. As yet unreported is the work of Cousineau with procaine and pentothal intravenously for thoracoplasties.

Intravenous procaine in anaesthesia is today a pregnant controversial incident, provoking opinions ranging from spontaneous ridicule to enthusiastic approval of its value as an adjuvant in anaesthetics.

Intravenous procaine was first used in our hospital in December, 1944, in conjunction with

spinal anaesthesia, in a case of a perforated ulcer for the relief of postoperative pain. It was used in a 1/1,000 solution in 5% glucose saline. Since that time, intravenous procaine has been used and observed in 870 cases, 70% of which have been in the past 15 months, in all types of anaesthesia, *i.e.*, spinal, spinal pentothal, nitrous oxide, ethylene, cyclopropane, cyclopropane-nitrous oxide inhalation; intravenous pentothal and balanced pentothal-cyclopropane. Cases have been unselected, ranging in age from 8 to 79 years; operative risks included grades 1 to 4 and the surgical procedures embraced head, neck, chest, abdominal and orthopaedic intervention. The procaine for intravenous use has been used in a solution of 1% or more commonly, a 1/1,000 solution prepared by adding one gram of procaine to one litre of normal saline; 5% glucose saline or distilled water. The 1/1,000 solution is preferred because pentothal, analeptics, curare or d-tubo-curarine can be added to the solution or injected into the tubing without any danger of an injurious precipitate being formed.

Observations on the use of intravenous procaine with various anaesthetic techniques are as follows:

*Inhalation anaesthesia.*—In 1945, intravenous procaine was used in a 1% solution, the dose 5 to 10 c.c. with the average 7 c.c., to correct cardiac arrhythmias occurring during cyclopropane anaesthesia. The rapid restoration of normal sinus rhythm encouraged us to attempt the prevention of this common complication of cyclopropane anaesthesia by the prophylactic use of procaine in a dilute solution in a continuous intravenous drip.

In radical breast operations, cholecystectomies, vagotomies and hysterectomies, relatively long and shocking surgical procedures which necessitate supportive fluid administration, the procaine, one gram to one litre of 5% glucose saline, in a continuous drip, to which since 1945 sodium pentothal has been added, is now an integral step in our balanced cyclopropane technique. The frequency of cardiac arrhythmias with cyclopropane anaesthesia became relatively uncommon.

With the adoption of the continuous dilute procaine, with or without pentothal, it has not been necessary to reduce the concentration of cyclopropane; dilute the mixture by the addition of oxygen or ether to correct any cardiac irregularities. In the limited number of cases

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in which arrhythmias have occurred, rapid restoration of sinus rhythm has been expedited by increasing the rate of the intravenous drip or by the administration of 50 to 100 mgm. of procaine in 1% solution into the tubing.

As experience with the dosage of intravenous procaine became extended and no ill-effects were apparent, it was observed that in patients who had received one-half gram or 500 c.c. of 1/1,000 solution, the gaseous requirements of cyclopropane to maintain surgical anaesthesia were noticeably reduced. In recent months following many cases in which the observation was corroborated, the procaine with pentothal in 1/1,000 solution is administered before induction with the gaseous agents is commenced. In this manner when surgical anaesthesia is attained, the patient has received a dosage of procaine between 400 and 500 mgm. and the maintenance of this stage was accomplished with less of the gaseous agents than was previously required before the intravenous use of procaine.

#### CASE 1

Trans-thoracic vagotomy for duodenal ulcer, aged 35; nitrous-oxide cyclopropane induction was followed by nasal-tracheal intubation and cyclopropane maintenance. During the surgical procedure when the lung was collapsed, cardiac irregularity in the form of extra-systoles occurred. One per cent procaine, 7 c.c. or 70 mgm. was given intravenously and within two minutes normal sinus rhythm was re-established. No further cardiac irregularities were noted during surgery.

#### CASE 2

Trans-thoracic vagotomy for duodenal ulcer, aged 26; pentothal induction was followed by nasal-tracheal intubation and maintenance was obtained by pentothal procaine 1/1,000 solution and nitrous-oxide oxygen in 70 to 30% concentration, with high flow of the gases. No cardiac irregularities were noted. The amount of pentothal and procaine used was one gram of each.

#### CASE 3

Cholecystectomy and appendectomy—aged 56, risk grade 3 due to myocardial damage caused by antecedent coronary thrombosis. This patient received pentothal induction 2½% followed by a maintenance which consisted of pentothal procaine 1/1,000 solution, cyclopropane and 2 c.c. of Squibbs' d-tubo-curarine. Surgery occupied 1½ hours with exploration of the common bile duct. At no time in this case was it necessary to administer cyclopropane at more than 200 c.c. flow of the gas per minute at regular intervals. The amount of procaine and pentothal administered was 1.75 gm. of each.

#### CASE 4

An elderly woman 79 years of age, grade 2 risk, with carcinoma of the breast. A radical amputation of the breast was performed. The anaesthesia consisted of induction with 2½% pentothal, a balanced maintenance accomplished with intravenous procaine pentothal in 1/1,000 solution and cyclopropane. The cyclopropane was delivered intermittently at a rate which did not exceed 200 c.c. per minute. The amount of procaine and pentothal utilized was one gram of each drug. No postoperative opiate sedation was required.

*Spinal: spinal pentothal anaesthesia.*—The use of intravenous procaine with these techniques revealed clinical evidence which has been difficult to assess and correlate. However, there seems to be sufficient merit to warrant the continued use and further investigation of the procedure.

The salient feature of intravenous procaine with spinal and spinal pentothal anaesthesia has been the reduction of the dose of the spinal drug in the aged patient of such a risk that spinal anaesthesia would be considered a technique to be avoided. With the procaine administration these patients withstand spinal anaesthesia and surgery remarkably well and their postoperative period is unusually comfortable and often uneventful.

In the young, grade 1 and 2 patient receiving intravenous procaine and pentothal no reduction in the dose of the spinal drug can be tolerated if adequate relaxation and anaesthesia are to be obtained. This contradictory clinical evidence might be explained by the variance in the pain threshold in the two different age groups or by the relatively more common emotional and nervous instability in the younger group. Nevertheless, in this younger group of good risk patients, intravenous procaine appeared to balance the spinal anaesthesia more satisfactorily in that the patients' condition throughout surgery and during the postoperative period was more favourable than in the cases in which procaine was not utilized. In the postoperative period it was noted that sedation was not required in the usual dosage or repetition.

#### CASE 1

A middle aged woman of 56 years considered a grade two to three risk because of pyloric obstruction underwent a total gastrectomy of 3½ hours' duration. The technique was continuous spinal anaesthesia with pontocaine, glucose, westocaine 0.1% balanced with pentothal procaine 1/1,000 solution in continuous intravenous drip. The initial spinal dose was 5 c.c. of the spinal drug and the second dose administered 1¾ hours later was again 5 c.c., constituting a total dose of 10 mgm. of pontocaine and 100 mgm. of novocaine. The amount of pentothal procaine over this period was 2.5 gm. of each. Other supportive measures included 750 c.c. of whole blood and continuous oxygen at 6 litres per minute delivered by nasal catheter. This case illustrates the small dose of pontocaine required when balanced with pentothal procaine solution intravenously. This patient made an uneventful recovery and the postoperative interval was characterized by the small requirement of opiate sedation, only three doses of ¼ of a grain of morphine being necessary.

#### CASE 2

An elderly man of 71 years of age, grade 3 risk, with carcinoma of the rectum had an abdominal perineal resection. Technique was as follows; a half hour before



the selected time of surgery, procaine-pentothal 1/1,000 solution was commenced in his room. On being brought to the operating room, the patient received a spinal anaesthesia, using pontocaine, glucose, westocaine in a 0.1% solution, the dose was 7 c.c. or 7 mgm. pontocaine and 56 mgm. of westocaine. The supportive treatment consisted of 500 c.c. whole blood, methedrine 1 c.c. intramuscularly and oxygen 6 litres per minute by nasal catheter. This shocking operation was performed in two hours and the patient was well sustained throughout. One and a half hours after being returned to his bed, he was reading the morning paper and smoking a cigarette. The postoperative sedation consisted of four doses of  $\frac{1}{2}$  grain of codeine hypodermically. The total dose of procaine and pentothal utilized was one gram of each drug.

#### CASE 3

Elderly man of 72 years of age, grade 2 risk, with strangulated inguinal hernia underwent operation for its relief. Anaesthesia consisted of spinal technique with the administration of 6 mgm. of pontocaine and 36 mgm. of westocaine, balanced with procaine-pentothal 1/1,000. The amount of procaine-pentothal used during surgery was 0.75 grams. This dosage produced adequate anaesthesia and relaxation for the execution of surgery.

*Intravenous anaesthesia.*—A small number of cases under pentothal anaesthesia received intravenous procaine. The procaine was in a dilution of one gram to a litre of 5% glucose saline or normal saline while pentothal was used in concentrations of  $2\frac{1}{2}\%$  and 1/1,000%. When the pentothal was used in  $2\frac{1}{2}\%$  solution, it was not injected into the tubing but by a second venipuncture because a precipitate is formed with procaine and pentothal in this concentration.

In burn cases analgesia was obtained with 1/1,000 intravenous procaine as described by Gordon.<sup>6</sup> When an amnesia was desired by the patient, pentothal was utilized in a  $2\frac{1}{2}\%$  by separate venipuncture or added to the procaine to give a 1/1,000 solution of both drugs.

Procaine-pentothal 1/1,000 solution has been used with one facial injury requiring surgery of one hour duration; two perineorrhaphies, six eye cases of over one hour duration, with satisfactory anaesthesia for the performance of surgery.

The use of intravenous procaine with pentothal anaesthesia has been limited because the surgical procedures have been of short duration. The technique, however, has merit to encourage further use in pentothal anaesthesia which might be of a long duration as is often the case in plastic and eye surgery. The combination of procaine-pentothal intravenously produces anaesthesia with a smaller dose of sodium pentothal than would be necessary if intravenous anaesthesia was the technique used.

#### CASE 1

A young adult 22 years of age with fractures of the left nasal bone, left maxilla, lacerations of the left forehead, left upper eyelid was admitted for surgery and given intravenous pentothal-procaine 1/1,000 solution to establish anaesthesia. Surgery required one hour and anaesthesia was adequately obtained with one gram of procaine and pentothal.

#### CASE 2

Plastic operation for entropion of the lower left eyelid in an adult male of 33 years of age, grade one risk receiving procaine-pentothal 1/1,000 solution for anaesthesia. Surgery required one hour and a half, anaesthesia maintained with 1.8 grams of sodium pentothal and procaine hydrochloride.

#### CASE 3

Adult male 35 years of age with trachoma and entropion of the lower lid. Anaesthesia for the two hour plastic repair of this condition was accomplished with  $2\frac{1}{2}\%$  pentothal induction and procaine-pentothal 1/1,000 maintenance. Total dose of pentothal utilized was 2 grams and procaine 1.5 grams.

*Postoperative therapy.*—Webster,<sup>8</sup> before a meeting of the Section of Anaesthesia at the Canadian Medical Association in 1945, reported a small series of cases in which intravenous procaine was used for the relief of postoperative pain and discomfort.

Procaine in 1/1,000 solution with or without pentothal in the same concentration has been used and observed in some 300 cases postoperatively. It is usually continued for 12 to 36 hours depending on the amount of procaine administered. The maximum dose has been three grams in a 36 hour period and to date this dose has not been exceeded. In two cases, in which intravenous procaine was used, the patient became apprehensive, excited and very restless and the drug had to be discontinued. The addition of one-half or one gram of pentothal to a litre of 1/1,000 procaine in 5% glucose saline or distilled water is sufficient to depress the central nervous system and these signs are not observed.

Intravenous procaine does not supplant or replace the postoperative sedation with morphine but can be considered an adjuvant to establish a more comfortable and pleasant postoperative interval. In cases receiving procaine 1/1,000 with or without the addition of pentothal, it has been observed that the postoperative sedative dose of morphine and its derivatives can be sharply reduced. Not only can the dosage of morphine be reduced but the interval of repetition can be extended from the usual every four hours to eight and even as long as twelve hours in many cases.

This observation is particularly applicable to patients in whom morphine is the cause of



nausea and dizziness and in whom a planned postoperative period with comfort can be exercised with intravenous procaine with or without pentothal.

**Complications.**—The complications of the intravenous injection of procaine are well known and readily recognized. The symptoms are referable either to the central nervous system with muscular twitchings preceding convulsive seizures or coma, or to the circulatory system with signs of collapse with a cold clammy skin and a rapid thready pulse. The severity of the clinical picture is dependent on the sensitivity of the patient to para-amino benzoic acid and on the amount, the rapidity of injection and the concentration of the drug entering the systemic circulation.

The accepted therapy today, of the complication, is the intravenous administration of sodium pentothal in 2½ or 5% solution. In the cases in which intravenous procaine has been observed, there has been only one case which presented sign of procaine toxicity. The absence of complications is probably due to the fact, first, that the majority of the cases received the procaine-pentothal technique and secondly, that the procaine was used in a dilute solution, *i.e.*, 1/1,000 concentration. No complications were recorded with intravenous 1% procaine providing the accepted dosage of 70 to 100 mgm. was not exceeded.

The case<sup>9</sup> presenting complications evidenced by muscular twitchings was a penetrating duodenal ulcer, receiving lumbar block anaesthesia balanced with sodium pentothal-procaine 1/1,000 concentration. As the operation was being concluded 1% procaine was administered in addition to the drip procaine to assure the postoperative comfort of the patient. After 12 c.c. of 1% procaine had been given, muscular twitchings in the face, neck and arms were noted. Cessation of the intravenous procaine was sufficient to arrest the twitchings. This patient had no postoperative pain or discomfort during the remainder of his stay in the hospital. No sedative of any type was necessary.

A further consideration in the occurrence of procaine complications is the recent investigations of Richards,<sup>10</sup> of Abbott Laboratories, in relation to procaine toxicity and vitamin C, regardless of the method of using procaine. He has disclosed that the depletion of vitamin C and starvation with improper fluid and electrolytic balance of the patient lowers his resistance

to the toxic action of procaine hydrochloride. Therefore, liberal amounts of vitamin C and glucose prior to the use of procaine is a procedure worthy of consideration. This is particularly important in elderly patients and in patients of poor nutritional status.

#### CONCLUSIONS

1. Intravenous procaine is a prophylactic and rapidly effective therapeutic measure for the prevention and correction of cardiac arrhythmias associated with cyclopropane anaesthesia.

2. Reduction of the gaseous agents, dosage of spinal drugs and intravenous pentothal, can be accomplished by the use of intravenous procaine either before or during the selected technique particularly in aged, middle aged and young poor risk patients.

3. The postoperative interval can be better balanced by intravenous procaine in that postoperative pain is alleviated and the requirement of opiate sedation and its repetition is not an imperative routine.

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### THE PRACTICAL APPLICATIONS OF HORMONE THERAPY IN GYNÆCOLOGY\*

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I AM specially appreciative of the honour you have done me in inviting me to give this lecture, in so far as I am the only lecturer in this series who is neither a Member nor a Fellow of your distinguished College. I am an endocrinologist, and as such it may be suspected that I shall be over-enthusiastic in the treatment of my subject. Let me therefore assure you at the outset that this will not be the case, for many of the patients I see have been sub-

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mitted to every form of hormone therapy without avail before they reach me, whereas those who respond readily to such treatment at such hands of their own doctors are unlikely to come my way. Indeed it is difficult sometimes to avoid becoming depressed by the slow progress this subject appears to make in the therapeutic field.

In order that one should not become unduly despondent over what I feel to be the slow progress of hormone therapy it is necessary to try to put the subject into its proper perspective, and to consider from what we know up to the present of the principles of gynaecological endocrinology, what, we *can* do, what we *should* theoretically be able to do, and what we *cannot* do.

*Selection of cases.*—To take an extreme, though not so very uncommon, example of what we cannot do, no endocrine treatment will terminate a phase of amenorrhœa if it happens to be due to pregnancy. In other words the first essential is a careful selection of cases, eliminating all those in which the symptoms are due to organic causes, before considering the patient suitable for endocrine therapy. This is the function of the gynaecologist and he should ensure, if necessary by examination under an anæsthetic or diagnostic curettage, that the amenorrhœa is not due to congenital abnormalities, the irregular bleeding to fibroids or polyps, nor the dysmenorrhœa to endometriosis.

*Principles of treatment.*—Having thus selected the case it then becomes necessary to observe such principles of treatment as our present imperfect knowledge has made it possible so far to lay down. These principles concern the choice of hormone, the dose given, and the time in relation to the phases of bleeding at which it is administered. It is not unknown for the *wrong hormone* to be used, as when gonadotrophins are injected in the treatment of irregular or excessive bleeding, or progesterone for dysmenorrhœa.

*Dosage* is still to a large extent empirical, but modern fashions are probably fallacious in many instances. For example, stilbœstrol is almost consistently used in over-doses, with the result that toxic effects are commonly experienced. Except when it is employed as a hæmostat it is seldom necessary to prescribe more than 1 or 2 mgm. daily, and frequently less than 1 mgm. is required. After the menopause more

than 0.5 mgm. daily is rarely called for. In such doses toxic effects are the exception rather than the rule. Other œstrogens, however, are nearly always given in too small doses. Thus diœstrol which up till now has been regarded as more potent than stilbœstrol has recently been shown to be  $3\frac{1}{3}$  times weaker, and hexœstrol, which on account of its apparently non-toxic character has enjoyed considerable popularity, is probably at least 10 times less potent than stilbœstrol, and may not produce toxic effects because in the doses usually employed it probably produces no œstrogenic effects. Some natural œstrogens, such as œstrone when given by mouth are very weak and really only suitable in controlling mild menopausal symptoms. Œstrone sulphate however appears to be considerably more potent. Progesterone is almost certainly injected in too small doses and not sufficiently frequently, and gonadotrophins would be more likely to be effective if given in thousands of units rather than in hundreds: chorionic gonadotrophins, though frequently employed in cases of functional menorrhagia, exert no influence, alone, on either the monkey or the human ovary, and it is only through the ovary that they could affect uterine bleeding.

*Timing* is another principle to which careful attention must be given in certain kinds of hormone therapy. For instance œstrogens are effective only if their administration is initiated in the first half of the cycle. Furthermore in the pre-menopausal woman they should not, except in special circumstances be given for longer than a fortnight or three weeks at a time, intervals of at least a week separating succeeding courses. Prolonged and continuous œstrogen therapy, especially if so potent an œstrogen as stilbœstrol is used in the fashionable dose of 1 mgm. three times a day, is strongly to be deprecated. At best it seldom achieves its object of regulating the cycle. It frequently induces unpleasant symptoms such as a bloated feeling and increase in weight due to fluid retention. It may give rise to severe and prolonged bleeding, and at the worst it may possibly cause inhibition, with permanent impairment of function, of the pituitary.

If we consider the possible results of hormone therapy in the three main types of menstrual disorder, amenorrhœa, menorrhagia and dysmenorrhœa, on the basis of what it can do, what it should be able to do—if we had the right



hormone preparations and used them correctly—and what it cannot do, we see that each of these conditions can be sub-divided into two groups, one of which cannot, or at any rate is less likely than the other to, respond to endocrine therapy. If we are to appraise the possibilities as well as the limitations of hormone therapy fairly, it is important to distinguish between these sub-groups.

*Amenorrhœa.*—There are, for instance, two chief types of amenorrhœa, the one primarily of pituitary, the other of ovarian, origin.

1. *Pituitary "shock" amenorrhœa.*—In the first case, the amenorrhœa is due to some, usually sudden, disturbance of pituitary function. Marked change of environment and mode of life, such as occurs when a girl leaves the sheltered surroundings of her home life to take up nursing or enter the Services; some emotional upset, such as the death of a close relative or an unhappy love affair; or failure to recover from the endocrine stresses of pregnancy, may lead to sudden and stubborn amenorrhœa, which may not even respond by withdrawal bleeding to large doses of œstrogen. There is frequently marked alteration in weight. In the severest cases there is a dramatic loss in weight, perhaps associated with symptoms suggestive of a functional type of Simmonds' disease. In most cases, however, there is considerable increase in weight, the distribution of the obesity being typical of pituitary deficiency.

In this type of amenorrhœa the gonadotrophic functions of the pituitary have been suddenly inhibited by impulses from the higher centres, or through the hypothalamus. How can œstrogens, in such circumstances, restore the endocrine balance, except by maintaining the uterine sensitivity until the ovaries resume their activity? How could gonadotrophins assist, except by substituting for the now inactive pituitary? Even so gonadotrophic therapy is but a crude caricature of the delicate and complex control which the normal pituitary gland exerts on the ovarian cycle. The lesion in this case is above the pituitary, and therefore beyond the scope of the endocrine system. What is required is something to stimulate the pituitary. The radiologist, the psychiatrist—perhaps with abreaction therapy—or nature may provide the cure, but not the endocrinologist.

2. *Ovarian deficiency amenorrhœa* ("menstrual instability").—The other main type of amenorrhœa is very different in origin as well as in manifestation. Here the woman gives a history of perhaps a late menarche heralded by one period which is succeeded by a prolonged phase of amenorrhœa, with subsequent periods at irregular and increasingly infrequent intervals. She may be tall and thin with long arms and legs and poorly developed breasts, a tendency to hirsutism, acne and acrocyanosis. Untreated she may enter upon an early menopause, perhaps in the middle or late thirties. Here the treatment certainly lies, theoretically at any rate, in the realm of endocrinology. Gonadotrophins should stimulate ovarian function, at least temporarily. That they do not, in our experience, is probably a reflection on the crudeness of their extraction and our ignorance of their usage. Theoretically œstrogens might lower the level of resistance of the uterus, and allow it to respond to the sub-normal activity of the ovary. It is even possible that small doses of œstrogen might stimulate the ovary. At any rate it is one's experience that in a small percentage of the milder cases a more regular cycle is restored by giving doses of œstrogen which will just produce withdrawal bleedings—about 1 mgm. of stilbœstrol daily for 14 days.

*Excessive and irregular bleeding.*—Gonadotrophins, progesterone, androgens and œstrogens have all been used in the treatment of this condition, and the sceptic may well ask for the rationale of such "hit-or-miss" therapy. The theory underlying gonadotrophic treatment is that excessive or irregular bleeding is an indication of deficient ovarian function which should be controlled by applying the appropriate pituitary stimulus. That modern gonadotrophic extracts do not produce that stimulus has already been indicated. Many combinations have been tried: serum gonadotrophin followed by chorionic gonadotrophin in various doses: both gonadotrophins overlapping in the middle of the artificial cycle: and, perhaps most popular of all though least likely to be effective, chorionic gonadotrophin, usually in homœopathic doses such as 100 I.U. given, almost inconsequently, once a week. Every method, from the most theoretically scientific to the frankly empirical, has proved disappointing in my experience. The use of the sex hormones, however is more justified. But



to understand however why oestrogen, which produces bleeding, should be used to stop bleeding; or why androgens which are antagonists to oestrogens should be used for the same purpose, or why progesterone which is complementary to the action of oestrogen should be expected to control oestrogenic bleeding, needs some explanation. The explanation is largely hypothetical. It is supposed that there are three levels of effective oestrogen concentration as far as uterine hæmorrhage is concerned. These are represented in the diagram (Fig. 1).

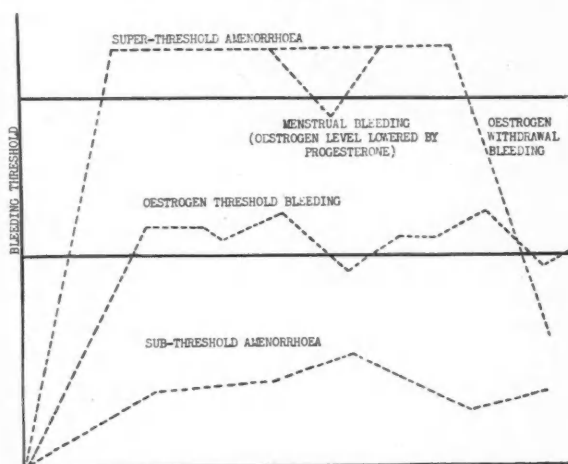


FIG. 1 OESTROGEN AND UTERINE BLEEDING.

An oestrogen level below the bleeding threshold will give rise to amenorrhœa ("sub-threshold" amenorrhœa). A level above the threshold will also give rise to amenorrhœa ("super-threshold" amenorrhœa). A drop in this level will induce bleeding, *e.g.*, the "oestrogen withdrawal bleeding" which follows a course of oestrogen in cases of amenorrhœa, and probably normal menstruation which is due to a drop in the effective oestrogen concentration. If the oestrogen concentration is within the bleeding threshold, constant or intermittent bleeding takes place. To stop bleeding, therefore, the effective concentration of oestrogen must be either raised or lowered. It may be raised by giving more oestrogen, or lowered by giving androgen, or by giving progesterone which renders the uterus less sensitive to oestrogen.

In practice there are two types of functional uterine bleeding, menorrhagia and metropathia. In the first there is some attempt at maintaining a menstrual rhythm, though bleeding is heavy and sometimes prolonged. Here the cycle is often ovular, though there may be evidence of deficient luteinization. Progesterone, however, is often unsuccessful in altering the

character of the bleeding. It should be given in doses of 10 or even 20 mgm. every other day during the premenstrual week. Androgens sometimes help, and may be administered orally in quite small doses such as 10 to 15 mgm. of methyl testosterone daily for up to 2 months. But on the whole this type of menstrual disturbance responds poorly to endocrine therapy.

In metropathia hæmorrhagical ovulation usually fails to occur and the endometrium remains constantly under the influence of oestrogen. On account of this, prolonged phases of amenorrhœa alternate with periods of bleeding sometimes profuse, sometimes merely trickling, which may last for weeks. Here progesterone is, in my experience, remarkably effective. When the bleeding has stopped 20 mgm. progesterone is given on alternate days for 4 doses. This is followed by a "progesterone withdrawal bleeding" which resembles a normal period. Further bleeding seldom occurs until a subsequent course of progesterone induces another progesterone withdrawal bleeding. This treatment is continued for about 6 months, after which recurrences may occur in 2 or 3 months, or the patient may continue with a regular bleeding pattern indefinitely. The large doses of progesterone apparently superimpose artificial cycles on the completely irregular bleeding which preceded the treatment.

**Dysmenorrhœa.**—From the point of view of endocrine therapy two types of dysmenorrhœa, however, may be distinguished; congestive and spasmodic. Congestive dysmenorrhœa is characterized by heavy bleeding, with clots, and pain lasting throughout the period. There is often a history of pelvic inflammation such as an appendectomy. The condition is presumably due to the contractions of the uterine muscle in the presence of the general vascular engorgement of the pelvis being translated into painful impulses. For this no hormone therapy is effective, though it is sometimes claimed that androgens help to diminish the congestion of the vessels.

In spasmodic dysmenorrhœa, however, the pain comes on at the beginning of bleeding or a few hours before. It is intense but transient and has usually disappeared by the second day. Direct observation of endometrial grafts in the anterior chamber of the eye in monkeys has revealed that immediately preceding the onset of the menstrual flow there is a period of some hours during which the graft is blanched on

account of the generalized spasm of the endometrial vessels. It is conceivable that the ischæmia may be so intense as to cause pain similar to the pain of angina or intermittent claudication. It would seem that the constriction and relaxation depend on the tone of these uterine vessels, and may be determined by the interaction of the ovarian hormones throughout the cycle. In practice at any rate the pain in many cases of dysmenorrhœa is relieved by the administration of œstrogen, provided it is applied in the correct doses and at the right time of the cycle. If the dose is high and given early in the cycle, a withdrawal bleeding will take place. This is usually scanty and different in character from a normal period—incidentally it is usually painless. But it is not the object of the treatment to produce these artificial "periods". A lower dose may give rise to a painless period of normal character and at the correct interval. If the dose is still lower either no effect is produced at all, or else the period is delayed, though when it occurs it is as painful as usual. If œstrogens are given late in the cycle, *i.e.*, after the 10th day, they are ineffective even though the dose may be high. Finally if the dose is too high, *i.e.*, 2 mgm. or more of stilbœstrol daily, there is considerable likelihood that ovulation will be inhibited.

#### SUMMARY

Certain aspects of hormone therapy in gynæcology have been chosen to illustrate the point that careful selection of the cases is essential if the results are not to prove considerably more disappointing than is to be expected anyway from a type of treatment which is still in its early days. For instance, in amenorrhœa of pituitary origin it is unreasonable to expect endocrine therapy to be effective, whereas if it is of ovarian origin small doses of œstrogens may re-establish regular cycles. In metro-pathia the response to regular courses of progesterone may be dramatic, whereas cases of menorrhagia are more disappointing in their results. In cases of congestive dysmenorrhœa hormone treatment is ineffective, though spasmodic dysmenorrhœa may be relieved by application of the correct dose of œstrogen given at the right time in the cycle.

#### AN X-RAY SURVEY OF ESKIMOS

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DURING the 1946 voyage of the *S.S. Nascopie*, the Eastern Arctic Patrol carried out an x-ray chest survey of all available Eskimos. The equipment consisted of a Picker portable unit complete with generator. The Eskimos were conveyed to the ship by the ship's cutter and all films were taken on board. The work was directed by the medical officer and done by a technician and one voluntary helper. Equipment for developing the films was also included and all but 200 were processed during the voyage.

Detailed reading of the films was made on the return to Ottawa and these were reviewed by three physicians experienced in chest radiography. While it was realized that it was impossible to make a final diagnosis from the x-ray films alone, as no follow-up was possible, an attempt was made, not only to recognize tuberculous lesions, but also to determine whether these were healed, active, or of questionable activity.

In all some 1,347 chest films were taken. One is impressed with the remarkably good quality of films obtained. While a few of the films were difficult to interpret, the number was small, considering the difficulties under which the survey party operated. This is the largest number of Eskimo films ever to have been obtained and represents a good cross section of the population of the territory covered. The total number of Eskimos in the Eastern Arctic is estimated at 6,000. The following areas and populations were not surveyed:

Ungava Bay Area .....	900
Fox Basin Area .....	400
West Side of Hudson Bay .....	500
Frobisher Bay and Blackhead Island....	500
	<hr/> 2,300

This leaves approximately 3,700 as the population sampled, of which 1,347 or 36% were x-rayed. This should give a fairly accurate picture of the incidence of tuberculosis in the Eastern Arctic. The census indicates that the

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male and female population is well balanced. Of those x-rayed, 746 were male and 657 were female. All age groups were represented in the survey except that very few under 5 were radiographed.

The films were examined and divided into three major groups:

1. The first group was classified as frankly tuberculous. These showed various degrees of parenchymal involvement, from minimal to far advanced or gross enlargement of hilar areas, presumably enlarged glands with or without parenchymal involvement, and no obvious evidence of calcification.

2. Those showing presumptive evidence of previous disease, now healed. No attempt was made to record minor evidences of previous tuberculous infection, *e.g.*, questionable Ghon's nodes, or minor degrees of hilar enlargement or calcification. However, a large number—64 or 4.7%—showed obvious evidence of enlargement and calcification of hilar and mediastinal areas or involvement of the parenchyma. Large irregular plaques were seen, varying in size from a large pea to a walnut, in hilar areas, parenchyma, or both. These were classified as presumptive evidence of previous disease now healed.

3. Those considered to be within normal limits. (Essentially negative.)

The number and percentages found in these groups were as follows:

	No.	%
1. Presumptive evidence of tuberculous disease (frankly T.B.). Active and activity undetermined .....	80	5.9
2. Presumptive evidence of previous disease, now calcified .....	63	4.7
3. Essentially negative .....	1,204	89.4
Total films examined .....	1,347	100.0

#### DISCUSSION

From the appearance of these films and the type of lesion found, one is justified in making certain observations. The first one is that the Eskimo is pretty thoroughly tubercularized. There is evidence of widespread infection in all areas touched by the *Nascope*. While there seems to be a slightly higher incidence in centres around the straits, as compared with northern areas, this is not great enough to warrant any final conclusion.

There seems to be ample evidence that the Eskimo shows a marked resistance to tuberculosis. The widespread evidence of previous infection showing gross calcification with no evidence of activity seems to bear this out.

Of the group who were probably active, while there were a few showing widespread exudative lesions, the majority would be classified as proliferative type. One has the impression that many of these would become arrested with sanatorium treatment, and it is more than likely if their activities could be

restricted and adequate diet available, that many would become healed and pass into the classification (2).

*The course of the disease in the Eskimo.*—Knowing the life and habits of the Eskimo and having studied the x-ray film of a representative group, one is tempted to speculate on the course of the disease in this people. There seems to be evidence that the infection is universal and that the dose is usually a heavy one. How would it be otherwise when the Eskimo is confined to a small igloo for so many months of the year? The marvel is that more do not develop the disease and succumb to it.

We see the greater proportion of films which, in the words of the radiologist, are classified as essentially normal. In others we see heavy hilar shadows with or without evidence of the primary focus. In others we see evidence of the calcified focus and gross evidence of calcification in the hilar areas. In others, we see well-defined calcified parenchymal lesions that have the appearance of healed adult type infection. The majority of others are productive in appearance and one would expect that in the course of time they will show evidence of healed disease, so evident in 4.7% of the films observed. Others will no doubt develop widespread disease that will prove fatal.

*Reason for heavy morbidity.*—The evidence seems to point overwhelmingly to massive infection rather than lack of resistance, and one is led to the conclusion that if infection could be controlled, tuberculosis could be controlled as readily in the Eskimo as in other races.

*Tuberculosis control program for Eastern Arctic.*—It would seem that the Eskimo presents no special problem in the way of tuberculosis control inherent in their particular race. They have evidently been tubercularized for many years and have survived as a race in spite of a high morbidity and mortality rate and with no attempt made to treat or segregate open cases. They appear to have withstood the onslaught of tuberculosis much the same as any other race would do without assistance in the way of segregation and treatment. Whether or not they have had longer experience as a race with tuberculosis, they seem to have been better able to resist it, judging by morbidity figures and x-ray appearance of lesions.

The problem then is the environment and the mode of life of the Eskimo, plus the present



insurmountable transportation difficulties. It would be a most difficult matter either to treat the Eskimo in the north, or to bring the sick ones outside for treatment. While a few who live around the settlements and are accessible to the two hospitals found in the Arctic might be treated, the only contact with many of them will be the annual visit of the *Nascopie*. One can readily see the problem in trying to examine, diagnose and decide which are to be taken aboard the ship, cared for on the remainder of the voyage and placed in institutions on the outside. Some are obviously hopeless cases, many will be loath to leave their families and go into voluntary exile. Those who have been sent out, particularly young children, lose their language and all connections with the north and become a problem of rehabilitation. They return quite unfit to take their place in the north.

The suggestion has been made that a centre be established in the north, such as at Southampton Island, for a sanatorium hospital, taking advantage of the air facilities and buildings already provided. The success of this would seem to depend on whether a practical air service can be developed, which could adequately serve this area. The difficulties and cost of maintaining such an institution, adequately staffed, present what may well be an insurmountable problem. It would seem to be desirable, however, to develop services already in the north and to organize nursing outposts where there is sufficient population to warrant such a service in places that can be visited by air throughout the greater part of the year.

This x-ray survey has been a very valuable one and gives a very excellent picture of tuberculosis in the Eskimo. More information is necessary as to the course of the disease and it is recommended that the survey be repeated annually. It would be extremely valuable to follow the disease in those showing abnormalities in the films.

The survey has demonstrated that it is possible to x-ray and interpret the films during the voyage and no doubt many favourable cases could be placed on treatment, either in the northern hospitals or brought outside by ship or plane.

The difficulties to be overcome are great and an adequate control program cannot be inaugurated immediately. Every effort should be made to study the problem and secure as much

information as possible which would have a bearing on long-term plans.

#### SUMMARY

1. A report of a chest x-ray survey of 1,347 Eskimos is outlined.
2. It is estimated that the group comprised 36% of the population sampled.
3. Presumptive evidence of tuberculous disease was found in 5.9%.
4. Presumptive evidence of previous disease now calcified was found in 4.7%.
5. There is evidence of widespread tubercularization of the Eskimo population and of resistance to tuberculosis as shown by the high percentage of calcified lesions.
6. The problems of treatment and isolation of open cases are discussed.

Acknowledgment of the great help given in making the survey possible is made to Mr. J. G. Wright, Superintendent of the Eastern Arctic, Department of Mines and Resources; Captain Jas. Waters and the entire personnel of the *S.S. Nascopie*; to Miss Margaret Lewis, x-ray technician; and to Dr. P. E. Moore, Director, Indian Medical Services, Department of Health and Welfare, under whose direction the survey was organized.

#### TREATMENT OF HYPERTHYROIDISM\*

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THE treatment of hyperthyroidism, so well established as a surgical problem prior to 1942, has once again become a controversial issue. The newer and safer antithyroid drugs of the thiouracil series are able to control hyperthyroidism over long periods of time with relative safety.

At present the safety and effectiveness of this method challenges surgery as the treatment of choice in selected cases of hyperthyroidism. If time establishes our hopes that these drugs will effect long-standing or permanent remissions in a significant percentage of the cases, a trial on medical treatment may well become standard practice in Graves' disease before thyroidectomy is advised.

Radioactive isotopes of iodine, now available at low cost from the Manhattan Project, are taken up selectively by the thyroid in hyperthyroidism and cause extensive or even complete destruction of the thyroid epithelium.

\* Read at the meeting of the Ontario Division of the Canadian Medical Association, May, 1947.

Since so much of the iodine is stored in the thyroid the radiation effects on the rest of the body appear to be negligible.<sup>1</sup> The ultimate effects of this intensive radiation of the thyroid have yet to be evaluated and hence this form of treatment has been reserved for complicated, carefully selected cases.

Propylthiouracil is much safer than thiouracil, and although perhaps not so effective in the doses commonly used, it still affords an excellent means of controlling hyperthyroidism without undue danger of side effects. Its toxicity appears to be between one-fifth and one-tenth of that of thiouracil. To my knowledge it has caused no fatalities to date, and in our experience with 218 cases there has been only one serious reaction, *i.e.*, exfoliative dermatitis. Leukopenia has been so rare that we do not insist on the weekly blood count but merely check the white and differential blood count a week after starting treatment and every two months at the time that the basal metabolic rate is determined. All patients are instructed in the significance of a sore throat, dermatitis, or fever.

The safety, convenience, and economy of this form of therapy necessarily raises the question of when, if ever, is thyroidectomy indicated in the treatment of hyperthyroidism? This question cannot as yet be answered because sufficient time has not elapsed to judge the permanence of the remission obtained following medical management. Nevertheless, we have gained certain impressions as to the type of cases which do not react favourably to medical management and in which thyroidectomy should be advised.

The medical treatment of hyperthyroidism with the antithyroid drugs is not as simple as it sounds, and considerable knowledge of the physiology of the thyroid and the pharmacology of the drugs is required if the patient is to be managed well. It is not practicable to give a supply of the drug to the family physician and instruct him to dispense it to the patient unless the physician be well versed in the treatment of thyroid disease. Too often the physician tends to deviate from the dosage schedule, to interrupt treatment, or to change to some other form of therapy.

The patient also must be co-operative and intelligent. Frequently as soon as she is feeling a little better she will discontinue taking the drug or will cut down on the dosage. It is

important, therefore, that the patient be co-operative and intelligent and also that she either live so conveniently close that she can return for periodic observation, or that she be attended by a well trained physician who is familiar with and sympathetic with the use of the antithyroid drugs. If these conditions can be met, medical treatment can be carried out satisfactorily over a period of a year or more, and we hope that in this way the chances of obtaining long-standing or permanent remissions can be increased. If these conditions cannot be fulfilled it is better to prepare the patient for operation and remove the thyroid.

In the beginning we used propylthiouracil in doses of 75 mgm. daily but soon found it necessary to increase the dosage to 150, 200, 300, and occasionally even to 400 or more mgm. Even these larger doses appear to be on the minimal side of the effective dose, because on several occasions there has been a prompt recurrence of symptoms and elevation of the basal metabolic rate when the dosage was reduced from 300 to 200 mgm. daily. Since the toxicity of the drug does not seem to be significantly increased in the larger doses, it may well be that much larger doses up to 500 or 600 mgm. eventually will be employed.

A second factor that suggests that doses of 200 mgm. daily are on the low side of what is required to effect a remission is the fact that few patients with these doses develop hypothyroidism. The basal metabolism often falls from +40 or +50 to +10 or +15 and hovers in this vicinity. Increasing the dosage often drives the basal metabolic rate to normal or occasionally to subnormal levels, while reducing it even a little may result in recurrence of the hyperthyroidism.

When the metabolism has fallen to zero or lower and all objective evidence of hyperthyroidism has been controlled, the disease is as completely and effectively controlled as it is by thyroidectomy. We have noted no symptoms referable to hyperthyroidism that have not been abolished in the patients whose basal metabolic rates have fallen to zero in response to medical management. On the other hand, there have been a few patients whose basal metabolic rates have not fallen to zero and even after receiving doses of 200 or 300 mgm. daily for four or five months have clinical evidence of residual hyperthyroidism. If the dosage were further increased or if treatment were



continued longer I believe the hyperthyroidism in these patients could be controlled, but we are feeling our way slowly and have only on one or two occasions given more than 400 mgm. daily. Most of the refractory patients have had severe hyperthyroidism and large goitres.

One of our objectives has been to evaluate the permanency of the remissions after a year or more of complete and continuous control under medical treatment. Since the dose of 75 mgm. daily, as initially recommended, proved insufficient to give a prompt and complete effect in the majority of cases we do not as yet have a sufficient number of patients who have been adequately treated and the drug withdrawn to justify any conclusions. However, from observation of patients who have of their own accord either cut down the dosage of propylthiouracil or have stopped taking it after having been well controlled for several months, it is quite apparent that there is a very striking tendency for prompt recurrences to take place. For this reason it cannot be stated that propylthiouracil is anything other than a safe and effective means of treating hyperthyroidism as long as treatment is continued. There have been a few isolated examples of patients whose hyperthyroidism has been in remission for a number of months after discontinuation of treatment, but these are patients who were treated first with thiouracil and whose hyperthyroidism was of mild or moderate severity. We do not as yet have data to prove that protracted remissions will be common, and there is no apparent means of predicting which case will obtain such a remission.

Side reactions have been few. In only 3 cases was it necessary to discontinue treatment because of toxicity. One patient, a man of 64 years of age with auricular fibrillation and arteriosclerotic heart disease, died suddenly after vomiting for a day. No blood counts were made, and there is no record of his having had any fever. He had taken the drug about a month without reaction, and there is little reason to suppose that his death is attributable to the use of propylthiouracil. There has been no case of agranulocytosis and so far as we know only one of granulopenia. This patient had a normal white blood cell count of 4,500 but only 25% granulocytes. There has been one patient who developed transient hives, 2 who became nauseated, one transient arthralgia, and one severe case of exfoliative dermatitis

after recovery from which a generalized lichenification of the skin took place. Interestingly enough, this patient took thiouracil for many months and propylthiouracil for nearly a year before the dermatitis developed. He has not as yet recovered sufficiently to enable us to test him to see if it is in reality the propylthiouracil that is responsible. Certainly, until proved otherwise, it must be assumed that the reaction is due to the drug.

Three patients have complained of numbness of the extremities while under treatment with propylthiouracil. One patient became very much disturbed emotionally after her hyperthyroidism was completely controlled, wept, and was hysterical, the chief complaint always being numbness. The emotional disturbances subsided promptly following withdrawal of the drug, but the numbness has persisted for several months. There was no alteration of blood chemistry and no sensory or motor changes were demonstrable. Questionable or mild toxic reactions have thus appeared in about 3% of the patients treated, and less than 0.5% have had serious reactions requiring hospital supervision.

At the present time it seems fair to say that the mortality and morbidity following treatment of hyperthyroidism with propylthiouracil over a period of one year is probably no higher than that of thyroidectomy in the hands of the most skillful surgeons and is much lower than that of thyroidectomy in the hands of the surgeon who only occasionally performs a thyroidectomy.

A group of 24 patients with hyperthyroidism have been treated with methyl thiouracil with excellent results. The remissions are obtained more quickly and appear to be more complete than those obtained with propylthiouracil, and to date no toxicity has been observed in doses up to 400 mgm. daily.

From the economic standpoint the patient who is treated medically is far ahead at the end of the first year. He need lose no time from work (provided he was able to work before treatment), he need have no more than four to six basal metabolic rate and white blood counts, nor more than six to twelve visits to a physician, no hospitalization, and no operative fee. The cost of propylthiouracil is not yet established, but it should not be high. The only question is, will this be just the beginning of a lifetime of medical treatment for hyperthy-



roidism, or will the remissions be permanent in a high enough percentage of the cases to warrant continuation of definitive treatment in the average case?

It is entirely possible that the treatment of hyperthyroidism may become comparable to that of peptic ulcer. The initial treatment may be medical except in certain cases of unusual severity in which experience has taught us that surgery is indicated. Surgical treatment in either ulcer or hyperthyroidism is indicated in those patients who (1) do not respond to treatment, (2) do not co-operate, (3) are subject to recurrences and do not wish to continue indefinitely on medical treatment, or (4) show signs suggestive of carcinoma.

Certain ulcers respond readily to medical treatment and some are apparently "cured" after a single course of intensive treatment. In most cases, however, the tendency to recurrence is always present and may appear if vigilance is relaxed. The situation as regards hyperthyroidism controlled by antithyroid drugs would appear comparable in many respects, except that the drugs used in the treatment of ulcer are known to be safe and the long-run safety of propylthiouracil is still unknown. If the numbness of which some of our patients have complained is indeed to be attributed to the drug its protracted use must be scrutinized carefully. Nor have we yet had sufficient experience to evaluate the long-range effects of the drug on the thyroid itself.

For these reasons I believe that for nodular goitre with hyperthyroidism and for patients with large diffuse goitres and severe hyperthyroidism thyroidectomy after appropriate preparation is the treatment of choice. There is no reason to believe that propylthiouracil is not effective in controlling hyperthyroidism associated with nodular goitre, but I am not yet prepared to recommend anything other than surgical removal of significant tumours of the thyroid. A trial of definitive medical treatment is warranted in patients with mild or moderate hyperthyroidism when associated with small or medium sized diffuse goitres, in recurrent hyperthyroidism when the morbidity of thyroidectomy is high, and in patients whose life expectancy is short, regardless of the type of goitre. In all cases the situation is explained to the patient frankly so that if she elects medical treatment and it fails to effect a cure, criticism cannot be made that time and money

were wasted in medical treatment when the disease could have been corrected in the beginning by operation. Similarly, the patients who are advised to have thyroidectomy performed are told of the status of medical treatment and it is explained that if they desire to give it a trial there are no contraindications.

To treat all patients with hyperthyroidism by thyroidectomy or all definitively by propylthiouracil would seem ill advised. It is quite possible that many of the patients who have been prepared for operation with propylthiouracil and subjected to thyroidectomy would have obtained a long-standing remission if treatment had been continued for a few months longer. Similarly, the attempt to treat all patients medically when the size of the goitre and the severity of the disease are such that, in the light of our present knowledge, little prospect of a permanent cure could be expected would seem to be equally ill advised.

One of the most striking features of the effects of the antithyroid drugs is the difference in the speed and completeness of the response in different patients. It is our impression, unsubstantiated as yet by adequate data, that those patients who are resistant, who require large doses, and who are incompletely controlled, tend to develop exacerbations very promptly upon withdrawal of the drug. The response of the patient to the drug may therefore be of some importance, and if this is the case it may be well to defer decision as to the choice of medical vs. surgical treatment until this response can be evaluated.

#### SUMMARY

1. Two hundred and eighteen patients with hyperthyroidism have been treated with propylthiouracil in the past year.

2. There has been one death, and this was probably unrelated to the use of the drug. There has been one serious complication, exfoliative dermatitis, with recovery.

3. Minor side reactions including granulopenia, urticaria, arthralgia, nausea, and sensations of "numbness" have occurred in less than 3% of the patients treated and have only twice necessitated interrupting treatment.

4. The dosage used, 200 to 300 mgm. daily, appears to be on the minimal side of the effective dose and in some instances does not appear to be sufficient to effect and maintain a remission.

5. The drug has not as yet been withdrawn from a sufficient number of patients to allow estimation of the percentage of cases in which long-standing remissions will occur. Judging from the prompt recurrences that have taken place in the patients who have of their own accord discontinued treatment after a few months of control, it does not appear that the incidence of remissions will be as high as had been hoped.

6. If the patient is co-operative and intelligent and can be observed by a physician who is familiar with the physiology of the thyroid and the pharmacology of the antithyroid drugs, treatment can be carried out safely and effectively over long periods of time.

7. When the patient is ignorant or unco-operative or cannot be observed periodically it is preferable to prepare the patient and perform a thyroidectomy.

8. Patients with small or moderate sized diffuse goitres with mild or moderate hyperthyroidism, patients with recurrent hyperthyroidism, and patients whose life expectancy is short, regardless of the type of goitre, may safely be given a trial on medical management for a year or more. If they respond favourably and prefer medical treatment this can be continued indefinitely. If they respond poorly or desire surgery a subtotal thyroidectomy should be performed.

9. Radioactive isotopes of iodine have been shown to be capable of controlling hyperthyroidism in most of the cases in which adequate doses have been given. Since the long-range safety of this form of treatment has not as yet been established it should be used with caution and in carefully selected cases.

10. Methyl thiouracil in doses of 200 to 400 mgm. daily appears to be more effective than propylthiouracil in producing a prompt and complete remission and in a small group of cases has not proved toxic.

#### REFERENCE

1. HERTZ, S. AND ROBERTS, A.: Radioactive iodine in study of thyroid physiology; use of radioactive iodine therapy in hyperthyroidism, *J. Am. M. Ass.*, 131: 81, 1946.

#### RÉSUMÉ

Rapport basé sur le traitement par le propylthiouracil en 1946 de 218 hyperthyroïdiens. Une seule mort fut enregistrée, d'ailleurs peu probablement imputable à la médication; une seule complication sérieuse fut notée: une dermatite exfoliative, du reste, guérie. Des ennuis mineurs ne furent signalés que dans 3% des cas. La dose quotidienne de 300 mg., dose minima, est probablement un peu faible. Le nombre des rémissions après

cessation de la médication sera plus faible qu'on l'eût espéré dès l'abord. Avec des malades intelligents et des médecins compétents la cure peut être poursuivie longtemps sans danger. En dehors de ces cas mieux vaut pratiquer la thyroïdectomie. Les isotopes radioactifs de l'iode peuvent maîtriser l'hyperthyroïdie chez la plupart des malades soumis à des doses suffisantes. On devra toutefois les employer avec prudence puisqu'on ne sait encore parfaitement leur seuil de tolérance après emploi prolongé. Le méthylthiouracil à la dose de 200 à 400 mg. par jour paraît être plus efficace que le propylthiouracil et il semble moins toxique.

JEAN SAUCIER

#### THE RH FACTOR\*

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DURING the past six years the blood agglutino-gen known as the Rh factor has aroused increasing interest all over the world. While its significance in the practice of clinical medicine and obstetrics is generally appreciated, its complexities are not as yet completely understood, and are still the subject of active investigation and research. Nevertheless, it is essential that all those engaged in the practice of obstetrics, pædiatrics, clinical pathology and blood transfusion therapy should have some understanding of the rôle it plays in the etiology of disease and in the production of intra-group hæmolytic transfusion reactions.

In 1940, Landsteiner and Wiener<sup>1, 2</sup> injected the red cells of the Rhesus monkey into rabbits, thereby producing an immune serum which was found to agglutinate the red cells of 85% of American white persons, but failed to react with the remaining 15%. Human bloods agglutinated by this immune serum were said to be Rhesus or Rh positive and those failing to react Rhesus or Rh negative.

It was well known that patients receiving repeated blood transfusions were particularly prone to increasingly severe hæmolytic reactions, even where the donor was one whose blood had caused no such reactions previously. In the investigations of three of these cases of hæmolytic transfusion reaction, Wiener and Peters<sup>3</sup> demon-

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strated an atypical agglutinin in the patient's serum which appeared to be identical with the experimental Rh sera of Landsteiner and Wiener. In each case, the recipient proved to be Rh negative and the reaction-producing blood Rh positive. It was postulated that the Rh negative patient had been immunized by antigenic Rh positive blood, an hypothesis which has proved to be essentially correct.

Hæmolytic reactions had also been reported after a single transfusion of apparently compatible blood, but in each case there was an associated current or recent pregnancy. As early as 1939, Levine and Stetson<sup>4</sup> had demonstrated an atypical agglutinin in the serum of such female patients and, moreover, had suggested that it might have been produced through isoimmunization to some antigen derived from the fetus.

Two years later, Levine<sup>5</sup> and his co-workers demonstrated that this liability to severe transfusion reactions in the puerperium was frequently associated with some abnormality of the fetus—usually hydrops, erythroblastosis or icterus gravis. They propounded the theory that the fetal disease as well as the mother's transfusion reaction was due to isoimmunization of the Rh negative mother by an Rh positive fetus. In their series, 90% of the mothers bearing affected infants were Rh negative, in marked contrast to the usual incidence of 15% in the general population. On the other hand, 100% of both affected infants and their fathers proved to be Rh positive. The rôle of the Rh factor in the etiology of hydrops fetalis, erythroblastosis and icterus gravis neonatorum has since been amply confirmed.

#### INHERITANCE OF THE RH FACTOR

At first it was assumed that the Rh factor was a single entity, inherited as a simple Mendelian dominant, the Rh negative gene (rh) being recessive.<sup>2, 6</sup> On this basis, it was possible to define genetically three classes of persons, as every human being would possess two Rh genes, one derived from his mother and one from his father. An Rh positive person may be either homozygous (*i.e.*, both genes the same) or heterozygous (*i.e.*, the two genes different). As the Rh negative gene (rh) is recessive, (*i.e.*, can exert its effect only when present in both chromosomes), it follows that the Rh negative person is always homozygous. The basic genetic formula for these three types (*i.e.*, genotypes) may be stated

as RhRh, Rhrh and rhrh. From the brilliant work of Race<sup>7 to 11</sup> in Great Britain and Wiener<sup>12 to 18</sup> in the United States, it soon became apparent that these three classes were not homogeneous. With the discovery of four types of Rh antibody, each with well-defined specificities, sub-division became possible, with seven recognized Rh genes. Each gene was associated with an antigen in the red cells of the owner which reacted with certain combinations of the four anti-Rh test sera, as shown in Table I.

In 1944, Professor R. A. Fisher,<sup>10, 19, 20</sup> from a study of the then known facts, postulated that each of the Rh genes is made up of three components (closely linked elementary genes), one from each of three allelomorphic pairs, arbitrarily designated C and c, D and d, E and e. Each of these simple genes gives rise to a single corresponding red cell antigen and each has a corresponding antibody specific for that antigen. From the above, it will be seen that the antibody anti-C agglutinates only the cells of a person possessing the gene C and therefore also the antigen C. Fisher's theory predicted the existence of an eighth allelomorph<sup>21</sup> and two additional antibodies, anti-d and anti-e. In 1945, Mourant found anti-e<sup>22</sup> and Diamond<sup>23</sup> has recently reported the finding of anti-d. Fisher's theory has, therefore, not only served to explain the known serological reactions but has proved to be an instrument of prediction. It provides, perhaps, the most satisfactory and logical nomenclature for Rh antigens and antibodies, incorporating and elucidating, as it does, the so-called "Hr" factor. Its general acceptance would do much to eliminate confusion in terminology.

TABLE I.  
ANTIGENIC STRUCTURE AND REACTIONS OF RH GENES

		Anti-					
		C	D	E	c	d	e
Rh <sub>1</sub>	(CDe)	.....	+	+	—	(—)	+
rh	(cde)	.....	—	—	—	(+)	+
Rh <sub>2</sub>	(cDE)	.....	—	+	+	(—)	—
Rh <sub>0</sub>	(cDe)	.....	—	+	—	(—)	+
Rh'	(cdE)	.....	—	—	+	(+)	—
Rh''	(Cde)	.....	+	—	—	(+)	+
Rh <sub>3</sub>	(CDE)	.....	+	+	+	(—)	—
Rh <sub>4</sub>	(CdE)	.....	+	—	+	(+)	—

From the reactions of the Rh genes given in Table I, the reactions of the genotypes can be built up. Thus, the genotype Rh<sub>1</sub>Rh<sub>2</sub> has an antigenic structure which may be designated CDe/cDE and the cells of this genotype will be agglutinated by the Rh antibodies anti-C, anti-D,



anti-E, anti-c and anti-e, but not by anti-d. In order to explain the antigen-antibody reaction related to the Rh genes, Fisher has postulated that their elementary genes occupy three adjacent loci on a chromosome. One of these loci can be occupied by the elementary gene C or its allele c, one by D or d, and the third by E or e. As the individual derives one chromosome of this kind from his father and one from his mother, his genotype is therefore determined by two sets of three elementary genes. This relationship can be shown diagrammatically (Table II).

TABLE II.  
FISHER'S THEORY OF RH INHERITANCE

Antibody	Loci on chromosome	Antibody
anti-C	C or c	anti-e
anti-D	D or d	anti-d
anti-E	E or e	anti-e

3 adjacent loci, each with 2 alleles, each allele with an antigen for which there is a specific antibody.

Recently, Race<sup>11</sup> and his co-workers have found an additional Rh antibody which has made it possible to recognize a third allelomorph at Fisher's C-c locus, designated by them as Cw. With the nine known Rh allelomorphs, forty-five genotypes are possible; some of these, predicted on the basis of Fisher's hypothesis, have yet to be found.

RH ANTIGENS AND ANTIBODIES

An appreciation of the complexities of the Rh factor has a practical importance. While immunization to the Rh factor occurs almost exclusively in the Rh negative person, the Rh positive individual can be immunized, either by pregnancy or transfusion, to an Rh antigen which he lacks (Case 1). The common practice of using only one anti-Rh serum, containing anti-D alone, for the typing of blood donors is to be deprecated, exposing the Rh negative patient, as it may, to possible isoimmunization by the Rh antigens C or E.

Rh antibodies occur in human serum in at least two distinct forms, those readily recognizable in saline dilutions in the test tube and the so-called "blocking antibodies"<sup>19, 24</sup> which are capable of combining with the positive cells without causing visible agglutination in aqueous dilutions. The blocking antibodies are demonstrable in a protein medium and their reactions are readily elicited when the test cells are suspended in a solution of 20% bovine albumin.<sup>27</sup> Human serum may contain a mixture of two anti-Rh agglutinins, most commonly anti-C and anti-D. In such mixtures, however, the anti-D is frequently in the blocking form. It is now evident that the presence of blocking antibodies does not indicate desensitization as was originally believed, but rather a high degree of isoimmunization.<sup>25</sup> The simple agglutinin appears early in the course of immunization. It is relatively fragile, even in the frozen state, and can be destroyed by heat. The blocking antibody, on the other hand, is considerably more stable. The majority of blocking antibodies are of the type anti-D, but Diamond and Abelson<sup>26</sup> have described blocking anti-C, anti-E and anti-e as well.

THE RH FACTOR IN BLOOD TRANSFUSION  
THERAPY

As will be seen from the above, the chief importance of the Rh factor lies in the fact that approximately 13 to 15% of our white population are Rh negative and are liable to produce antibody if the Rh antigen is introduced into their circulation. The first time Rh positive red cells are introduced into the circulation of an Rh negative person they survive for the normal period (100 to 120 days). Apart, therefore, from the Rh negative patient who has been immunized by pregnancy, the danger of hæmolytic reaction lies in repeated transfusions, as 85 to 87% of prospective donors will be Rh positive.

TABLE III.  
RH ANTISERA AND THEIR REACTIONS TO THE MORE COMMON RH GENOTYPES

Rh-Antisera (Fisher)	Rh-Antisera (Wiener)	Rh <sub>1</sub> Rh <sub>1</sub> CDe/CDe	Rh <sub>2</sub> rh cDE/cde	Rh <sub>2</sub> Rh <sub>2</sub> cDE/cDE	rrrh cde/cde	Rh'rh Cde/cde	Rh''rh cdE/cde
Anti-D	anti-Rh <sub>0</sub>	+	+	+	—	—	—
Anti-C	anti-Rh'	+	—	—	—	+	—
Anti-E	anti-Rh''	—	+	+	—	—	+
Anti-c	anti-Hr'	—	+	+	+	+	+
Anti-d	anti-Hr <sub>0</sub>	—	+	—	+	+	+
Anti-e	anti-Hr''	+	+	—	+	+	+
Mixed antisera							
Anti-D+C	anti-Rh <sub>0</sub> '	+	±	+	—	+	—
Anti-D+E	anti-Rh <sub>0</sub> ''	+	+	+	—	—	+

Isoimmunization of the Rh negative recipient is variable in onset and may occur after a single transfusion with Rh positive blood, even an intramuscular injection during infancy.<sup>28</sup> As yet, no method has been devised by which an immunized person can be desensitized or his antibodies neutralized. Once isoimmunization has been produced, it is apparently permanent and hæmolytic reactions may appear, and may be expected to increase in severity, with each subsequent transfusion of Rh positive blood. In two surveys of Rh negative Canadian and American ex-servicemen who had been transfused as war casualties, Whittaker<sup>29</sup> and Diamond<sup>30</sup> demonstrated that 43 to 46% of these had been immunized by blood transfusion. With the female Rh negative patient, particularly the multipara, the danger involved in indiscriminate transfusion is even greater, as she may have been previously immunized by an Rh positive fetus.

Now that reliable anti-A and anti-B grouping sera are available to hospitals, probably 80 to 90% of all hæmolytic transfusion reactions are due to Rh incompatibility.<sup>31, 32, 33</sup> While this is particularly likely to occur in maternity practice, it should be remembered that severe and even fatal hæmolytic reactions have occurred in men immunized by previous blood transfusions. Reactions due to transfusion of Rh incompatible blood are, however, generally milder than those associated with incompatibility related to the ABO groups, but they can vary in degree from failure of the patient's hæmoglobin to show the expected rise and the disappearance of Rh positive cells from the circulation to jaundice, hæmoglobinuria, oliguria, uræmia and death.

Because of the danger of hæmolytic reaction in a patient already isoimmunized by pregnancy or transfusion, as well as the possibility of initiating an Rh sensitization which would later prove prejudicial to a normal pregnancy, wherever possible, patients of either sex should be transfused with Rh compatible blood. A direct match of the donor's cells against the patient's serum, as well as the grouping and Rh typing of both donor and recipient, should precede every transfusion of whole blood and the circumstances must be very exceptional to justify this omission.

The direct match should be performed at both room and incubator temperatures. As patients with blocking Rh antibodies are the most likely

to suffer severe hæmolytic reactions, wherever the recipient is Rh negative or there is other reason to suspect Rh isoimmunization, the direct match of the patient's serum should also be set up with a suspension of the donor's cells in 20% bovine albumin. All tests macroscopically negative should be checked microscopically.

Where multiple transfusions are contemplated, a direct match should be performed on a freshly drawn sample of the patient's serum on each occasion, unless it can be definitely established that the patient has not been exposed to the Rh factor. In the latter event, it is probably unnecessary to use a fresh sample of the patient's blood unless more than seven days have elapsed. Should it be suspected that the patient has already been immunized by pregnancy or transfusion, samples of the patient's serum should be taken for direct match at more frequent intervals, as the immunized body can be stimulated to increased antibody production within 24 to 48 hours after the introduction of antigenic blood.

In an emergency, it is usually practicable to sustain the patient with plasma until adequate grouping and direct matching of whole blood can be performed. Should it be considered that such a delay would endanger the life of the patient, the use of unmatched, Rh negative, Group O blood carries the least risk, particularly in the obstetrical case where the past clinical history is suggestive of Rh isoimmunization.

In the selection of the Rh negative bloods for transfusion, all not agglutinated by anti-D (anti-Rh<sub>0</sub>) should be further examined with sera containing anti-C (anti-Rh' or anti-Rh'<sub>0</sub>) and, if available, with anti-E (anti-Rh'' or anti-Rh''<sub>0</sub>). Otherwise, the rarer bloods containing the antigens Cde (Rh') and cdE (Rh'') will be diagnosed as Rh negative and may cause a hæmolytic reaction if transfused into an immunized Rh negative patient. The use of Cde (Rh') blood as Rh negative is particularly dangerous, as approximately half anti-Rh sera of human origin contain anti-C. With cdE (Rh'') cells, the risk is much less, as human sera containing anti-E are relatively rare.

On the other hand, patients whose cells give a negative reaction with anti-D (anti-Rh<sub>0</sub>) serum should receive Rh negative blood, even though their cells react with anti-C or anti-E, as not infrequently such patients are immunized by the Rh antigens they lack.

#### THE RH FACTOR IN ERYTHROBLASTOSIS FETALIS

Hydrops fetalis, icterus gravis neonatorum, erythroblastosis fetalis and hæmolytic anæmia of the newborn are now recognized as having a common etiology and, therefore, may be considered as clinical variations of one disease entity,<sup>34</sup> commonly designated in the British literature as "hæmolytic disease of the newborn". In the vast majority of cases, the condition is due to the isoimmunization of the mother to an antigen present in the erythrocytes of her fetus. The antibody so produced in the mother's serum crosses the placental membrane to gain access to the fetus' circulation, destroying its cells and producing intravascular hæmolytic. Almost invariably, the Rh factor is the antigen responsible, although other blood agglutinogens, including those of the ABO groups, may be incriminated.

Hæmolytic disease of the newborn must be considered an important cause of infant mortality. Haldane<sup>35</sup> has stated that it is responsible for more deaths than any other inherited disease and possibly more than the total for all inherited diseases. The frequency of its occurrence has been estimated as 1:150 pregnancies. Unfortunately, a great deal of misinformation on the subject has been published in both the medical and lay press and practical conclusions have been drawn which cannot be supported by scientific facts. Rh negative women have, in some instances, been advised not to marry Rh positive males. It is obvious, however, that all Rh-negative-Rh-positive matings do not produce affected infants, as such unions will represent one in every ten pregnancies. That isoimmunization does not invariably occur with this combination may have several explanations. In affected families, it is common to have one to three normal children before there is evidence of erythroblastosis. The disease, therefore, may never appear in the small modern family, although there is a latent possibility. Diamond<sup>36</sup> has shown, moreover, that there are marked individual differences in sensitivity to isoimmunization by the Rh factor.

The method by which fetal antigen gains access to the maternal circulation during pregnancy has not been definitely established. A number of observers<sup>29, 36</sup> have noted a high incidence of bleeding during previous pregnancies, and this may indicate a break in the

placental barrier, permitting the introduction of the fetal antigen.

Isoimmunization of the Rh negative person by transfusion of Rh positive blood has already been discussed. Perhaps the most severe forms of erythroblastosis are encountered in the children of women who have been sensitized by previous transfusion.<sup>37</sup> Where the disease appears in the first pregnancy, there is frequently a history of previous blood transfusion. Even the intramuscular injection of Rh positive blood in infancy is sufficient to initiate the isoimmunization of the Rh negative female, resulting many years later in the appearance of erythroblastosis in her firstborn.<sup>36, 38</sup>

Unfortunately, it has become common practice to attribute the majority of complications of pregnancy in the Rh negative woman to Rh incompatibility, particularly where there is a history of abortions and miscarriages. The Rh factor can be incriminated only where there is adequate proof that isoimmunization has actually occurred. The recognition of a variety of Rh antibodies in maternal blood, occurring in the two distinct forms already described, has made it possible to detect isoimmunization to the Rh factor in almost 100% of the mothers bearing affected infants.<sup>39</sup>

Perhaps the most satisfactory single test of isoimmunization due to pregnancy is to incubate the mother's serum with her husband's or her affected infant's red cells in a suspension of 20% bovine albumin. Such a test will, of course, detect the presence of blocking antibody as well as those active in saline dilutions.

Without question, the routine Rh testing of every expectant mother would be a valuable safeguard, not only in protecting her against a foreign Rh antigen should she require transfusion at labour but by sounding a warning of possible abnormality in her fetus. It is hoped that before long such routine tests will be a practical procedure in every antenatal clinic. Maternal blood which is positive to a potent anti-D (anti-Rh<sub>0</sub>) test serum normally requires no further investigation unless there is a clinical history suggestive of erythroblastosis in previous pregnancies. If, on the other hand, the expectant mother's blood is Rh negative, an attempt should be made to secure a specimen of her husband's blood. If he is found to be Rh negative as well, normally no further investigation is indicated. If, on the other hand, he is found to be Rh positive, maternal sera should,



at regular intervals throughout pregnancy, be examined for Rh isoimmunization, including, where possible, suspensions of the husband's cells for such tests.

Evidence of isoimmunization is most likely to be elicited after the thirty-second week of pregnancy, but can frequently be detected before this where the woman has been sensitized by previous pregnancy or blood transfusion. An effort should always be made, particularly in the multipara, to detect blocking antibodies as well as those readily demonstrable in saline dilutions.

Where the four necessary test sera are available, determination of the maternal and paternal genotypes may give valuable information as to prognosis.<sup>37, 40, 41</sup> Where it can be established that the Rh positive husband of an Rh negative woman is a homozygote, his children will all be Rh positive (Case 2). If, therefore, the Rh negative woman has been immunized to the Rh factor, and has borne affected children, only in very rare instances will she produce an unaffected child by a homozygous Rh positive mate at any subsequent pregnancy. Case 3 is an exception to this rule for which there is no obvious explanation. If, on the other hand, it can be established that the Rh positive husband is a heterozygote, there will be a 50% chance of his producing an Rh negative, and therefore unaffected, child (Case 4).

From the above, it will be seen that it is possible to anticipate the development of erythroblastosis in the fetus and to take appropriate steps for the treatment of the infant as soon as it is born. Prompt transfusion with Rh negative blood will save the majority of infants<sup>20, 43, 44</sup> except those in which the central nervous system is already involved by kernicterus, in the development of which exposure to maternal antibodies, with concurrent liver damage, during the latter weeks of pregnancy is probably a potent factor. Much has been written as to the desirability of performing early Cæsarean section wherever the mother can be shown to have been immunized.<sup>25</sup> Other authorities,<sup>42</sup> however, consider this too radical, advancing the argument that prematurity of the infant and the operative risk to the mother outweigh any advantages that could thereby be gained. If, however, a high degree of immunization to the Rh factor is indicated by the appearance and rise of titre of blocking antibodies, particularly where the father is a homozygote, the

prognosis is very grave. In such cases, induction of labour, whether by Cæsarean or otherwise, should be considered as soon as the fetus can be regarded as viable, thus reducing the child's exposure to damaging antibodies and possibly preventing the serious sequelæ of erythroblastosis. The recently developed replacement transfusion, in which the affected infant's blood is gradually replaced with Rh negative blood, may offer an even greater measure of success in the treatment of these cases.

There is no evidence that kernicterus, once developed, is in any way influenced by transfusion therapy. Children surviving kernicterus commonly show mental backwardness or imbecility, usually associated with spasticity and frequently with choreiform or athetoid movements. The majority, however, die with central nervous system manifestations on the fourth or fifth day of life.

Until adequate Rh investigation of every expectant mother is done as a routine procedure, cases of erythroblastosis will appear without preliminary warning. In the absence of suggestive obstetric history or a knowledge of the parents' Rh types, certain clinical features of the disease should be borne in mind. Jaundice appearing within a few hours of birth, tending to deepen rapidly, is significant, as physiological jaundice, usually milder in degree, rarely appears under 48 hours of delivery. A rapidly deepening jaundice, accompanied by drowsiness and failure to feed satisfactorily, with perhaps a high-pitched cry, justifies the infant's immediate removal to a hospital where adequate transfusion facilities are available. The infant should be accompanied by a test tube containing 15 to 20 c.c. of its mother's blood. Immediate steps should be taken to establish the Rh grouping of both mother and infant. The mother's serum should be examined for Rh antibody, particularly the blocking form. In an effort to do this, the maternal serum is incubated with a suspension of the infant's cells in both saline and 20% bovine albumin. As the infant's serum should also be examined for Rh antibody, it is strongly recommended that samples of cord blood should be collected for laboratory examination in every case of suspected erythroblastosis.

Where it can be established that the child of an immunized Rh negative woman is Rh positive, its serum contains blocking antibody and

its cells have been sensitized by Rh antibody as shown by the Coombs test,<sup>45</sup> immediate transfusion with Rh negative blood, preferably by the replacement technique, is indicated.<sup>36</sup>

It is important to realize that in the treatment of infants suffering from erythroblastosis the blood must be transfused into the circulation. Subcutaneous or intramuscular injection is useless. If transfusion is performed at birth or shortly after, the umbilical vein is convenient for the purpose. At a later stage, a scalp vein or the internal saphenous vein may be employed. Satisfactory results have been obtained by transfusion into the bone marrow of the tibia, although this procedure may present technical difficulties.

Blood used for the transfusion of these infants should be of the same ABO group and Rh type as the mother, which, except in rare instances (Case 1) will be Rh negative, and should be matched against the mother's serum. As maternal antibody is likely to persist in the infant's circulation for at least seven to ten days after delivery, this rule should be followed for all transfusions undertaken during the first two weeks of life.

Hæmatological examination at birth or shortly after may show no evidence of anæmia or other significant abnormality. In the untreated case, however, anæmia is likely to develop rapidly, with the appearance of early primary erythroblasts in the peripheral blood. While a single transfusion of Rh compatible blood is usually sufficient to arrest the average case of erythroblastosis, the hæmoglobin level should be checked daily during the first two weeks of life and the transfusion repeated should anæmia develop.

It is well known that the breast milk of the highly immunized Rh negative mother is likely to contain Rh antibody.<sup>46, 47</sup> In the opinion of many authorities,<sup>37, 48</sup> the affected child should not be breast fed by its mother for the first two weeks of life.

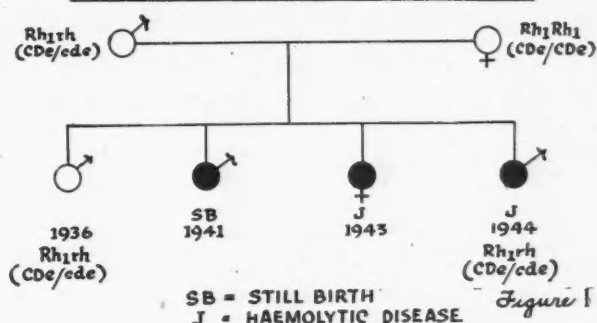
Finally, it should again be emphasized that every effort must be made to confirm the diagnosis of erythroblastosis before treatment is instituted. Not only should it be established that the mother has been immunized by an Rh antigen but also that the maternal antibody is incompatible with the infant's red cells. Clinical diagnosis must, therefore, be confirmed by the laboratory if the optimum results are to be obtained.

## CASE HISTORIES

### CASE 1

An Rh positive woman immunized by the antigen c (Hr), with anti-c demonstrable in her serum. The infant born in 1944 was transfused with Rh positive blood lacking the antigen c, i.e., blood of genotype Rh,Rh, (CDe/CDe). The child, however, died on the fifth day with kernicterus.

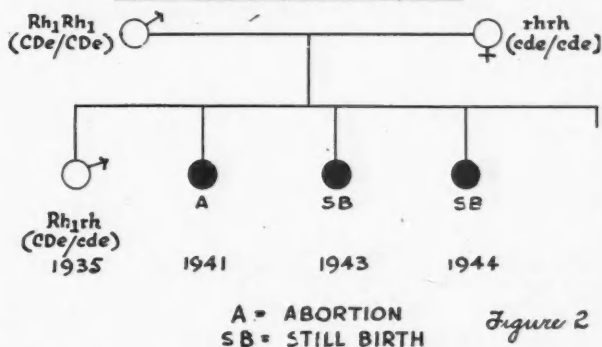
### HETEROZYGOTE Rh POSITIVE MATING



### CASE 2

An Rh negative woman immunized to the Rh antigens C and D. Both anti-C and anti-D were present in her serum during the last pregnancy, anti-D in the blocking form. As her husband is an Rh positive homozygote and she is already highly immunized, the prognosis for future pregnancies is poor.

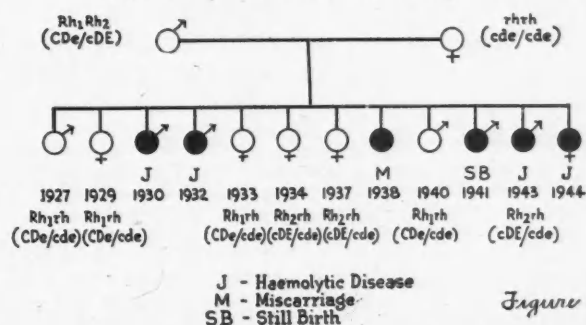
### HOMOZYGOTE MATINGS



### CASE 3

An Rh negative woman immunized to the Rh antigen D, with a high titre of anti-D in her serum during her two most recent pregnancies. Although the husband is an Rh positive homozygote, i.e., the elementary gene D present on both chromosomes, he has fathered unaffected Rh positive children subsequent to the birth of infants suffering from erythroblastosis. This occurrence is very rare. The infant born in 1943 recovered after a single transfusion with Rh negative blood.

### HOMOZYGOTE MATINGS



## CASE 4

An Rh negative woman immunized to the Rh antigens C and D, with both anti-C and anti-D demonstrable in her serum, the latter in a blocking form. As the father is an Rh positive heterozygote, the family includes both Rh positive and Rh negative children. The twins of the 1943 pregnancy both died of erythroblastosis.

## HETEROZYGOTE MATINGS

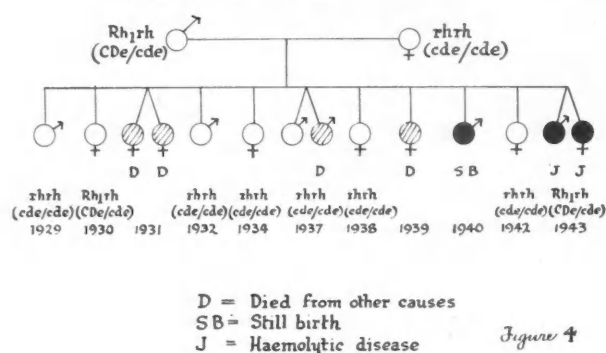


Figure 4

## SUMMARY

The Rh factor is present in the red cells of about 87% of the American and British white population, and is of practical importance almost exclusively to persons lacking it.

Approximately 45% of Rh negative persons of either sex may become immunized to the Rh factor by transfusion with Rh positive blood. An Rh negative woman mated with an Rh positive male may be immunized to the Rh factor by one or more pregnancies involving an Rh positive fetus. A subsequent transfusion of Rh positive blood to Rh negative patients immunized by either transfusion or pregnancy may result in a severe or even fatal haemolytic reaction.

A pregnant Rh negative woman, who has been immunized to the Rh factor by either transfusion or previous pregnancy, can produce antibodies in her serum capable of crossing the placenta and thus developing erythroblastosis in her unborn Rh positive child.

The recognition of a variety of Rh antibodies in maternal blood, occurring in at least two distinct forms, has made it possible to detect Rh sensitization in almost 100% of mothers bearing affected infants. The early testing of maternal blood for the Rh factor, therefore, and the periodic examination throughout pregnancy of the sera of Rh negative women mated with Rh positive males, is of great practical value in prognosis by determining the presence and degree of Rh immunization.

Where a high degree of immunization to the Rh factor is indicated by the presence of blocking antibodies in the mother's serum, particularly where the father is a homozygote, induc-

tion of labour should be considered as soon as the fetus can be regarded as viable.

Encouraging results have been reported by transfusing the affected infant with Rh negative blood as soon after birth as possible. The more recently developed complete substitution or replacement transfusion may prove even more satisfactory.

To obtain optimum efficiency in the diagnosis and treatment of erythroblastosis, there must be the closest co-operation of obstetrician, paediatrician and clinical pathologist.

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## ACUTE INTESTINAL OBSTRUCTION\*

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THE problem of acute intestinal obstruction is and has always been a most vital one. Before the turn of the century, it was a most depressing problem because of the high mortality it carried. In 1944, however, Veal stated that the mortality rate of acute intestinal obstruction is largely the mortality rate of delay and rises with each hour that proper treatment is delayed. It therefore becomes necessary for us to arrive at an early diagnosis and institute the proper treatment without too much procrastination.

### CLASSIFICATION

Intestinal obstruction may be classified in the first place with regard to location: high or low in the small bowel, in the colon, closed loop occlusion with sterile, mildly infected or heavily infected loops and strangulation of short, medium or long loops. Or, it may be classified according to cause. The causes may be mechanical, the result of certain developmental errors such as atresia and imperforation, or due to inflammation, trauma, vascular obstruction or neoplasm. Obturation may be caused by gallstones, fecoliths, worms or foreign bodies. Obstruction from adhesions or bands is a very common cause; these may be congenital, inflammatory, traumatic or neoplastic but postoperative bands are the most common type. Herniae, the most common cause of obstruction, may be either external or internal. And then again, there may be volvulus or intussusception. Obstruction may also be due to nervous imbalance, either spontaneous or post-traumatic, and in these cases we have a distension which becomes exceedingly troublesome. Vascular obstruction is due to thrombosis or embolus, mostly to thromboses in the mesenteric area.

Groups of cases have been collected by McIvor, Souttar and Vick, both in the United States and in England, which prove that external herniae comprise the greatest percentage of cases reported. They range from 44 to 47% of the total. Adhesions and bands were next in frequency, from 18 to 35%. Neoplasms

which are chiefly in the large bowel account for 10 to 13% with intussusception from 5 to 15% and volvulus from 2 to 4%. Mesenteric thrombosis was responsible for 3% and all other causes, including gallstones, as high as 4%. Tumen states that volvulus is higher in Europe than in America. All forms are more common in males except gallstones which predominate in women. Malignancy is the most common cause after the fiftieth year.

### PATHOLOGY

The pathology of acute intestinal obstruction is very important. If the obstruction is high in the small bowel, there is a loss of fluid and with the fluid, the electrolytes are also lost, particularly sodium chloride. The sodium ion is the important factor. The fluid in the interstitial tissues becomes concentrated. The sodium is extracted from the cells by osmosis and dehydration is established. Fluid and electrolytes are introduced parenterally to restore the balance. If water is introduced by mouth a certain amount of the mineral elements pass into this solution on account of the osmotic pressure and the electrolytes are therefore withdrawn from the tissues into the solution in the stomach. This further depletes the mineral elements. If the stomach is washed out it should be done with normal saline.

Distension in high obstruction is not marked but when the obstruction is low, distension increases in proportion to the amount of ileus that exists and the amount of fluid that collects. If infection is present in the intestinal content, gas is formed. This, plus a large amount of swallowed gas, which Dr. Wangenstein places as high as 68%, causes an increase of gas in the bowel with more marked distension. The bowel is further distended by an increase of fluid. This is, to a large extent, due to secretion—at least in the early part of the disease—because the bowel secretes from 7,000 to 8,000 c.c. daily. If distension and pressure continue, there is a further collection of fluid from the capillaries. Edema of the small bowel occurs, nutrition is affected and fluid may eventually pass through the bowel wall into the abdominal cavity.

Strangulation may, and frequently does, cause gangrene and more fluid—particularly toxic fluid—filters into the abdominal cavity, although the situation is not entirely clear, the mechanism by which intestinal obstruction

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causes death may be summarized as a change in the fluid balance, by loss of electrolytes, by distension, permeability of the bowel and loss of plasma. All of these add up to the condition which we call shock.

#### SYMPTOMATOLOGY

The symptomatology resolves itself into three important symptoms: (1) Pains that are cramp-like and come in waves due to the increased activity of the bowel and the effort it makes to force the content past the obstruction. The cramps come at fairly regular intervals and it is my impression that the higher in the bowel the obstruction occurs, the more rapidly they come. They are usually felt in the epigastrium or in the mid-abdomen. Another factor is the development of distension. (2) Vomiting. If the obstruction is high, the vomiting is more profuse. If low or in the colon, vomiting is less marked or at times may be absent. Distension with pain or cramps and no vomiting usually means obstruction in the colon. (3) Constipation is an important symptom. This may be acute or may have existed for some time.

The examination too is of importance. As we look at the patient we see the skin is dry, usually with some pallor and the membranes also are dry. The pulse early shows very little change but later becomes smaller and more rapid. The blood pressure at first may be very little affected. If the blood pressure is low, it is of bad prognostic significance. Distension varies with the location of the obstruction and the length of time since the obstruction has developed. Visible peristalsis may be present but usually means a slowly developing obstruction. Peristaltic sounds present a high-pitched note. These are quite pronounced unless there is a development of ileus, which may occur. Abdominal tenderness is one of the earliest and most characteristic signs of developing strangulation. A patient should be seen and examined frequently so that the exact condition is known at all times.

A procedure which is sometimes used in arriving at a diagnosis is the aspiration of the abdominal cavity, using a relatively small needle—gauge No. 20 or No. 21. The recovery of bloody fluid indicates strangulation.

The next factor I wish to mention in arriving at a diagnosis is an x-ray of the abdomen. First there should be a scout plate and then a plate

with the patient standing, if this is at all possible. Fluid levels with gas formation in the small bowel—unless it is in a child—is of great significance. The plates should be taken anteroposteriorly, laterally and in the oblique position. A tube may be left in the stomach but an enema, in my opinion, should never be given immediately before an x-ray is taken. In examining a patient one should always look for free air.

If one is suspicious of obstruction in the large bowel, thin barium may be given as it can be siphoned off if it is not passed voluntarily. With a Miller-Abbott tube in position one can empty the tube and introduce a little thin barium, but the amount must be small so that one can locate reasonably accurately the point of obstruction.

The diagnosis must be made from the history, both present and past, signs as just stated and x-rays as outlined. Laboratory investigations can also be used. A rising hæmoglobin, either by the ordinary test or the hæmocrit, will give some information. There may be a moderate increase in the white blood cells. The blood chloride, urea nitrogen and carbon dioxide combining power of the blood also may help; the latter indicates an increase in alkalosis. Intestinal obstruction must be differentiated from acute appendicitis, acute cholecystitis, ruptured viscus, external herniæ, acute pancreatitis and a twisted pedicle of an ovarian cyst.

#### TREATMENT

Treatment, we believe, should be early. It is particularly important that early operation be performed in strangulation, either in a hernia, thrombosis of the mesentery or a volvulus. Wangenstein states, however, that there is a mortality of treatment as well as of disease. The object of treatment is to remove the cause, to restore the lumen of the bowel and to correct the general body disturbance. This is done by replacing fluids and electrolytes, maintaining satisfactory blood levels and also preventing hypoproteinæmia. Glucose, saline and amino acids are all available today and they should be used in preparing the patient for operation as well as during the postoperative period. If the circulation is showing signs of failure, the bowel distended and it is difficult to locate the site of the obstruction without too much manipulation, an ileostomy or colostomy should be performed, the bowel may be exteriorized

or, if possible, anastomosis may be done. If the condition of the bowel permits and the obstruction can be located, it should be released at once, whether the obstruction be caused by bands, adhesions or volvulus.

In intestinal obstruction, if time will at all permit, one should use the latest method of decompressing the intestine in the form of a Miller-Abbott tube. In the beginning it was very difficult for us to get it by the pylorus. By the use of a little mercury—2½ to 5 c.c.—it is possible to get it past the pylorus in a very short time. We follow this with the x-ray and in the last few months have been very successful in postponing immediate operation unless it happened to be strangulated obstruction.

Two cases I recall, both in the country and both night cases, the one a woman of 57 years and the other a man of 33. They had both been going for some time before I saw them and it was imperative that something be done at once. We gave the patients intravenous injections, emptied the stomach according to the Wangenstein method, and opened the abdomen. The first case, that of the woman, had been obstructed for three days. Peristalsis was visible but not very definitely heard with the stethoscope. There was a definite ladder pattern. The patient had some distension, but not marked, and looked very ill. At operation about three feet of bowel was removed and a side-to-side anastomosis performed in the small bowel, and she made a good recovery. In the man, we removed about four feet of bowel from the ileocaecal junction and re-anastomosed, side-to-side, between the lower end of the caecum and the ileum. His recovery was uneventful. About two weeks later his father came in to pay the bill and in answer to my query as to his son's progress, he said he had eaten a big dinner of roast chicken the day before. I am mentioning this merely because when one is not closely in touch with the patient anything may happen and eventually cause disaster, where if closely watched one can be more certain of a good result.

In closing, I should like to note the mortality statistics reported by Ravdin and Johnson in the *American Journal of the Medical Sciences*. In 1873 the mortality was given as 73%; in 1908 as 60%; in 1931 as 17.1%. I know that some men are reporting lower figures than these and it is my hope that the decrease may still further continue.

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### STUDIES ON AMŒBIASIS

#### A CLINICAL STUDY OF CHILDREN PASSING CYSTS OF *Entamoeba histolytica*\*

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IN a recent paper<sup>2</sup> the writer pointed out that human infections with *Entamoeba histolytica* are not rare in Canada; in fact, about 250,000 Canadians harbour this parasite. It was shown also that the number of endogenous cases of acute amœbic colitis and metastatic amœbiasis was small, but of greater importance as a medical problem were the low-grade chronic infections and the apparently asymptomatic "cyst passers". In an attempt to evaluate the clinical manifestations of these "cyst passers" a study was made of a group of male children in an orphanage showing a high incidence of infection with *Entamoeba histolytica*.

**Materials and methods.**—A total of 93 children was studied in the present investigation. They were inmates of an orphanage where they had lived from two to four years, and in a few cases, longer. Their ages ranged from 7 to 11 years, and they all lived under similar conditions of food, clothing, shelter, and recreation. The children were divided into two groups of 46 and 47, respectively. The first group of 46 children was found infected with large strains of *E. histolytica*; the second group of 47 was not infected with this parasite. Positive diagnoses were made by the zinc-sulphate centrifugal-flotation technique, confirmed in many cases by

\* Contribution from the Institute of Parasitology, Macdonald College, McGill University, with financial assistance from the National Research Council of Canada.

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wet-smear preparations, iron-haematoxylin permanent-mount preparations, and culture techniques. The children in the non-infected group were considered free of infection after a total of six stool specimens examined by the zinc-sulphate centrifugal-flotation technique were found negative. Many of the children in both groups were infected with *Giardia lamblia* and *Enterobius vermicularis*, as well as the common species of non-pathogenic intestinal amoebæ found in man.

A comparison of the age distribution in the two groups of the children under study showed that the infected group had an average age of 9 years plus 9 months, with a standard deviation of 9.5 months. The average age of the non-infected group was 9 years plus 8.5 months with a standard deviation of 9.5 months. Thus the age distribution was almost identical in the two groups.

The study may, for convenience, be divided into three parts: the first simply deals with the weights and heights of the children in each group, the second is concerned with the clinical laboratory tests, and the third entails a clinical study. Clinical laboratory tests include total white blood cell counts, differential counts, haemoglobin determinations, and sedimentation rates. The clinical studies include a brief physical examination to exclude serious manifest signs of disease which might prejudice the comparative results, and a clinical history which deals with the general behaviour, playing habits, resistance to fatigue, nervousness, as well as a detailed history of symptoms referable to the gastro-intestinal tract. In addition, wherever possible, information was obtained on the past medical history of each child. The medical history was provided by a nurse who was, and has been in charge of the children from the time of their arrival at the orphanage. This informa-

tion was derived from her personal experience with the children, her medical records, and further information which she obtained from the personnel in charge of each dormitory. This nurse was considered competent and reliable.

## RESULTS

*Height and weight.*—The heights of the non-infected group ranged from 40.0 to 58.0 inches, with the mean height at 50.20 inches. The children in the group infected with *Entamoeba histolytica* showed heights which ranged from 43.8 to 55.0 inches, with the mean height at 49.99 inches. Thus the children in the infected group were an average of 0.21 inches shorter.

The mean weight of the non-infected group was 58.80 lb., while the mean weight of the infected group was 58.04 lb. However, because of the slightly different age distribution in the two groups, a more significant method of comparing the weights is to calculate the difference in weight for each child from a normal standard based on the height and age of that child, and then to compare the average difference from the normal, in both groups. Such a calculation showed that the children in the non-infected group were an average of 0.5 lb. underweight, while those in the infected group were 0.1 lb. underweight.

*Clinical laboratory tests.*—The results of the laboratory tests are summarized in Table I. A study of the table shows that the mean total white cell count in the non-infected group is 14,130 cells/c.mm., as compared with an average count of 11,320 for the infected group. Thus, while both counts are high the infected group shows an average count which is 2,810 cells/c.mm. lower than the control group. The differential counts show that while all components of the white blood cells occur in greater numbers in the non-infected group, the difference in the

TABLE I.  
THE WHITE BLOOD CELL COUNTS, HEMOGLOBIN LEVELS, AND SEDIMENTATION RATES FOUND TO OCCUR IN TWO GROUPS OF CHILDREN, ONE NON-INFECTED AND THE OTHER INFECTED WITH *Entamoeba histolytica*

	Non-infected group		Infected group		O D S E
	Arithmetical mean	Standard deviation	Arithmetical mean	Standard deviation	
Total white count....	14,130	2,994	11,320	2,130	5.10
Neutrophiles .....	6,514	2,000	4,920	1,543	4.28
Lymphocytes ...	6,405	2,081	5,391	1,577	2.73
Eosinophiles ....	704	500	628	411	0.79
Monocytes .....	465	314	363	224	1.80
Basophiles .....	42		18		
Hæmoglobin .....	86.9%	6.8	86.5%	6.5	0.39
Sedimentation rate ..	8.9 mm./hr.	6.4	10.7 mm./hr.	6.6	1.367

total white cell counts is primarily due to the polymorphonuclear neutrophile series.

The mean hæmoglobin levels in the two groups are almost identical, 86.9% for the non-infected as compared with 86.5% for the infected group.

The mean sedimentation rate for the non-infected group is 8.9 mm./hr., while the mean sedimentation rate for the infected group is 10.7 mm./hr. or 1.8 mm./hr., greater.

#### CLINICAL STUDIES

The physical examination of the subjects studied did not reveal any marked signs of disease. Most of the children in both groups showed chronically inflamed throats with enlarged tonsils, and an associated cervical lymphadenopathy. About one-fifth of the children in both groups showed advanced dental caries; in about one-half the teeth were good, while the remainder showed varying degrees of mild dental caries. From a purely subjective grading of the development and nutritional status of the children under study, it appeared that the infected group as a whole showed a degree of development and nutritional status inferior to that of the non-infected group. However, as the actual weights of the infected group showed that they were at least as great as those in the non-infected one, it is felt that this subjective impression of development and nutritional status should be discounted.

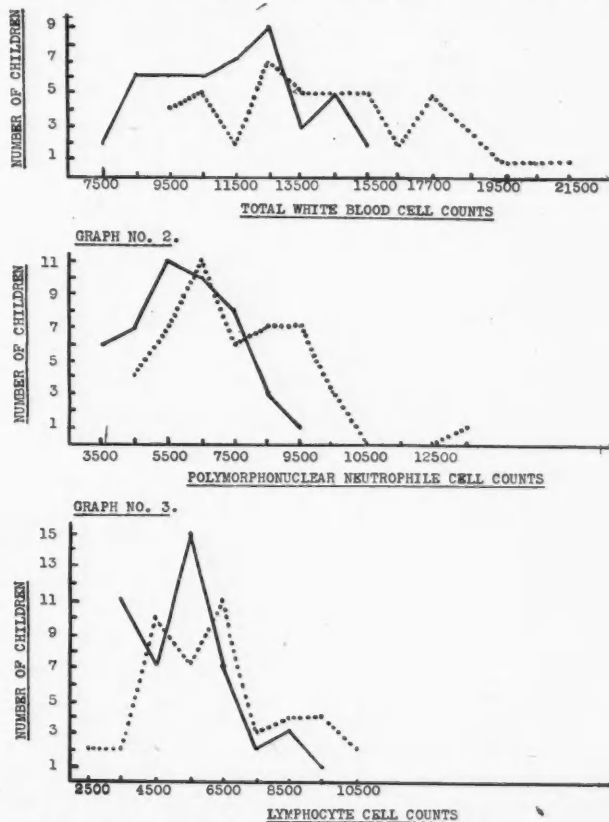
In the general history only one symptom appeared which was of any significance, the symptom of easy fatigability. In the control group of 47, four children were named as tiring too readily, while in the infected group 12 of the 46 children showed this symptom. A few of the children were stated as showing excessive nervousness and irritability, but this symptom was evenly distributed in both the infected and non-infected groups. With regard to symptoms of the gastro-intestinal tract, the infected group revealed eight children showing a total of 20 symptoms as compared with only one child showing a single symptom in the control group. Symptoms shown by the children in the infected group were as follows: 4 children showing anorexia, 6 children with nausea and vomiting, 5 children with abdominal pain, and 5 with abnormal bowel movements. The anorexia was a relatively constant symptom; the nausea and vomiting as well as the abdominal pain recurred at varying intervals in the different children. The abnormal bowel movements were character-

ized by alternating diarrhoea and constipation in three children, and constipation and diarrhoea in each one of the remaining two. Only one symptom, anorexia, occurred in the control group, and that was present in only one child.

#### DISCUSSION

The average height of the children infected with *Entamæba histolytica* approaches the average height of the control group very closely, and the fact that the infected group is 0.21 inches shorter, on an average, cannot be considered significant. A comparison of the weights in the infected and control groups shows that the infected group is at least as heavy on an average as is the control group. We are free to say then that the infection with *E. histolytica* did not cause a reduction in weight or a decrease in height in the groups under investigation.

The mean total white cell count of the infected group is 14,130 while the control group shows a mean count of 11,320. Both of these counts are high and the former is beyond the normal upper limits. A study of the differential counts shows that the primary reason for the high



Graph 1.—Histograms showing the distribution of total white blood cell counts, polymorphonuclear neutrophile cell counts and lymphocyte counts in two groups of children, one non-infected and the other infected with *Entamæba histolytica*. The solid line refers to the infected children; the broken line to the non-infected group.

counts is the large number of lymphocytes. The absolute lymphocytosis is probably explained by the chronic throat infections seen in the large majority of children in both groups. However, this factor is a constant in both the infected and the control groups and any differences we may observe in the two groups should be due to the presence of *Entamoeba histolytica*. A comparison of the mean total counts, and of the various components of the white blood cell series, in the infected and control groups is made in Table I and the significance of their differences calculated by dividing the standard error into the observed difference. The results show that the mean counts of the total white blood cells, the polymorphonuclear neutrophils, and the lymphocytes are all significantly higher in the non-infected group. The differences observed in the mean eosinophile, monocyte and basophile counts in the two groups are not great enough to be considered significant. (We can say, therefore, that the infections with *Entamoeba histolytica* resulted in a lowering in the number of the total white blood cells of the host, which was primarily due to a suppression of the polymorphonuclear neutrophil leukocytes and to a lesser extent of the lymphocytes.)

The mean value for the haemoglobin levels in the control group is 86.9% as compared with 86.5% for the group harbouring *Entamoeba histolytica*. The very slight drop in haemoglobin seen in the infected group as compared with the control group is readily explained by chance sampling and it must be accepted then, that the children infected with *E. histolytica* show a haemoglobin level which is on the average as high as that seen in the control group.

The sedimentation rates in the control group show a mean value of 8.9 mm./hr., while in the group infected with *E. histolytica* the mean value of the sedimentation rate is 10.7 mm./hr. Thus the children in the infected group show a sedimentation rate which is an average of 1.8 mm./hr. greater than the control group. However, it is unlikely that this difference is due to the infection with *E. histolytica* as the test for significance arrived at by dividing the standard error into the observed difference indicates that it can be explained by chance variations (see Table I).

The results of the physical examination of the group under study do not reveal any signs of disease peculiar to the group infected with *E. histolytica*. However, the symptoms do show

that three times as many children in the infected group had a history of ready fatigability as do those in the control group, that is, 12 children as compared with four. That this difference is significant has been determined by calculating the value of chi square from the 2 x 2 table as used by Grant.<sup>1</sup> The presence of 8 children in the infected group showing<sup>20</sup> symptoms referable to the gastro-intestinal tract as opposed to one child showing a single symptom in the control group suggests very strongly that the parasite may play a minor but definite clinical rôle in the cyst-passing group of infections. It was of interest to note that 5 of the children in the infected group showing symptoms, present a syndrome of nausea and vomiting, abdominal pain, and abnormal bowel movements, which recurred at intervals. This complex, suggestive of a chronic recurring appendix, has been described by several authors in non-dysenteric amoebiasis.

Very little work has been reported on the blood picture of the so-called "carrier-state" in amoebiasis. Sapero<sup>3</sup> reported on the results of a study carried out on 61 patients passing cysts of *E. histolytica* and compared them with similar studies on a control group of 61 persons. He found there was no significant differences in the haemoglobin levels, the erythrocyte counts, or the differential counts. Unfortunately, total white blood cell counts were not done. The results obtained in the present study agree with Sapero's findings as regards the haemoglobin levels, but the relative reduction of polymorphonuclear neutrophils seen in the infected children apparently was not seen in the infected adults studied by Sapero.

Many authors have stressed the clinical aspects of non-dysenteric amoebiasis and have considered the infected person as subject to a long and varied list of symptoms. That some of these symptoms are due to the amoebic infection cannot be denied. On the other hand, it is equally true that the majority of these writers base their opinions on subjective impressions, and that critical, analytical studies in this regard are all too few. The known propensity of the human subject to neurasthenia with its accompanying complex of symptoms make clinical studies of any disease where the symptoms are as vague and ill-defined as those stated to occur in "carrier" amoebiasis of value only when compared with the results obtained from the study of an experimentally acceptable control group.



Even the use of specific therapy with amelioration of symptoms is not always significant evidence in these cases because the psychological effect of any active treatment on a patient suffering from a neurosis is well known and may influence the results. Sapero<sup>3</sup> in his study on non-dysenteric amœbiasis included a control group. According to his results the infected group did show a significantly greater number of symptoms than did the control group. It was of interest to note that the symptoms and signs he found most commonly in the infected group were abdominal pain, abnormal bowel movements, and abdominal tenderness. In a further group of non-dysenteric amœbiasis infections who had been hospitalized previous to diagnosis, nausea was found to be a common symptom as well. Results obtained in the present investigation fit in well with the above findings and emphasize the fact that a syndrome simulating chronic appendicitis may be encountered in non-dysenteric amœbiasis.

It is readily admitted that the possibility of getting an adequate clinical history from children in the age groups studied is next to impossible. On the other hand, when such symptoms are complained of, and when signs are observed spontaneously, they are probably of greater significance than those elicited by specific questioning. For this reason it is believed that the symptoms recorded in the present investigation do not exaggerate the symptomatology in the group studied.

The assistance given by Miss Catherine Sutherland and Miss Rita Numinville of the Ste. Anne's D.V.A. Hospital during the course of the study is gratefully acknowledged.

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The absurd paradox of this era is constituted by the prodigious achievements of medicine on the one hand and the destructive fury of war on the other. That such miracles should be performed in the alleviation of human suffering and the preservation of life while war spreads disease and death is a fateful coincidence that deserves deep study and thought.—R. C. Hutchison, *J. Am. M. Ass.*, 134: 1482, 1947.

### SURVEY OF INTESTINAL PARASITES IN REPATRIATED PRISONERS OF WAR FROM HONG KONG

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THE men studied in this survey were army personnel taken prisoner at Hong Kong, repatriated to their homes in Quebec and the Maritime Provinces. When repatriated a quick provisional survey was done, mostly in army hospitals, and those requiring treatment were detained in hospitals at that time. An initial screening was done by special personnel and it can be safely assumed that all active cases and heavily-infected carriers were detected and treated.

In order to determine whether or not an appreciable number of these ex-prisoners of war were still carrying pathogenic parasites after several months in Canada, it was decided to form a special survey group and to recall as many of the men as possible regardless of symptoms, or lack of symptoms. This survey was made between April and October, 1946.

The following system was adopted: the men were admitted to hospital for 6 days; normal stools were examined every morning for 3 days; a purge was given on the morning of the fourth day and a fresh specimen examined on a warm stage; two more normal specimens were examined on the fifth and sixth days.

For normal specimens the stools were washed and the standard zinc sulphate flotation method used for concentrating for cysts. In addition direct microscopic examinations of faecal material were done routinely, before the concentration method was applied.

The identification of protozoan parasites was based on their morphological appearance in D'Antoni's iodine and in hæmatoxylin stained smears. Trophozoites were examined in normal saline on a warm stage of the microscope. Their morphology, the type of motion, the ingestion of red cells and the appearance when fixed smears were stained with hæmatoxylin were considered in their identification. Men in whom pathogenic parasites were found, were treated appropriately and "negatives" were discharged on the sixth day.

In the above systems and techniques there was nothing remarkable except for the observa-

tion that in a number of cases pathogenic parasites were only found after purging. In many of these, the parasites were found in the specimens of the fifth and sixth days and not in the purge specimen itself. Results were as follows:

Cases in which parasites were found in normal stools .....	231
Cases in which parasites were only found after purging .....	41

The following is a summary of the over-all results:

Total number of patients examined .....	453
Total number of stool samples examined .....	2,315

	Number	Percentage
1. Patients not showing any parasites	145	34.00
2. Patients showing non-pathogenic parasites only .....	187	41.28
3. Patients showing pathogenic parasites .....	121	26.72

The following distribution of parasites was found:

#### PATHOGENIC PARASITES

	No. of cases	% of pos. cases (i.e. out of 121)	% of total groups (i.e. out of 453)
<i>Endamæba histolytica</i> .....	32	26.44	7.06
<i>Giardia lamblia</i> .....	43	35.53	9.49
<i>Ascaris lumbricoides</i> .....	41	33.88	9.05
<i>Ankylostoma duodenale</i> .....	19	15.70	4.19
<i>Enterobius vermicularis</i> .....	4	3.30	0.88
<i>Hymenolepis nana</i> .....	1	0.82	0.22
<i>Strongyloides stercoralis</i> .....	1	0.82	0.22

(The above percentages are individual because of the fact that some of the patients showed mixed pathogenic infections).

#### NON-PATHOGENIC PARASITES

<i>Endamæba coli</i> .....	165	36.42
<i>Endolimax nana</i> .....	102	22.51
<i>Iodamæba butschlii</i> .....	11	2.42
<i>Chilomastix mesnili</i> .....	14	3.09
<i>Trichocephalus trichiuris</i> .....	78	17.21
<i>Trichomonas hominis</i> .....	1	0.22

Workers experienced in dealing with repatriates from the far east, suggest that pathogenic parasites of various kinds are more commonly found in men who give a history of severe, typical amœbic dysentery and also in men who have low-grade recurring intestinal upsets, asthenia, anorexia or failure to regain weight and strength. On this basis, the following analysis was made of the survey results:

	No.	% out of 213
Number of cases with history of more or less definite amœbic dysentery .....	213	
Showing pathogenic parasites (including <i>E. histolytica</i> ) .....	55	25.82

Showing <i>Endamæba histolytica</i> .....	16	7.51
Number of cases having had any kind of acute or chronic intestinal upset since return to Canada .....	21	% out of 21
Showing pathogenic parasites (including <i>E. histolytica</i> ) .....	5	23.80
Showing <i>Endamæba histolytica</i> .....	3	14.28
Number of cases complaining of asthenia, anorexia or general failure to regain normal weight and strength .....	95	% out of 95
Showing pathogenic parasites (including <i>E. histolytica</i> ) .....	13	13.68
Showing <i>Endamæba histolytica</i> .....	8	8.42
Number of cases where history is clear enough to indicate definitely that the patient has had no history of typical amœbic dysentery and no complaints (as above) since return to Canada..	110	% out of 110
Showing pathogenic parasites (including <i>E. histolytica</i> ) .....	16	14.53
Showing <i>Endamæba histolytica</i> .....	4	3.63

(As a number of the case histories have not been completed, plus the fact that a patient's history may fall into more than one of the above four groups, the numbers do not tally with the number of patients examined in the survey).

Because *E. histolytica* is recognized as the most troublesome pathogen of the group analyzed, the following comparative figures may be of interest:

	Percentage
Patients without definite histories of acute amœbic dysentery and without symptoms since returning to Canada, occurrence of <i>E. histolytica</i> .....	3.6
Patients without symptoms but giving a definite history of typical amœbic dysentery, occurrence of <i>E. histolytica</i> .....	7.5
Patients who have had vague symptoms (as outlined above) since returning to Canada, occurrence of <i>E. histolytica</i> .....	9.5

It must be borne in mind that the group surveyed had been screened on their arrival in Canada, and that any having suggestive symptoms or positive stool findings had been hospitalized and treated. Consequently the group reported upon did not have definite symptoms of parasitic infestation and were known not to be heavy carriers.

Dr. T. H. Williams has reported the findings from repatriated Hong Kong prisoners of war returned to the Winnipeg district and he has given the incidence of *E. histolytica* as being 13%.<sup>1</sup> It is difficult to compare his figures with those of the present survey because he started the examinations soon after the men returned and his group included a number of cases with active symptoms.

Comparison of the present group with the incidence of *E. histolytica* in the general popula-

tion of Canada is somewhat more instructive. Dr. M. J. Miller has recently reviewed the available data and in his summary, states that the evidence points to an incidence of *E. histolytica* of approximately 2%.<sup>2</sup> Individual reports give 1 and 3% in surveys of the general population and as high as 37% in institutions. Its incidence in the group reported here is 7.06%. The only sub-group which approaches the *E. histolytica* incidence quoted for the general population, is that of men having no history of typical amœbic dysentery and no complaints since returning to Canada (3.6%).

It is felt that the comparative figures presented tend to support the suggestion that the rather vague symptoms listed in the tables are quite often associated with the carrying of pathogenic parasites (up to 23.8%) and that in an appreciable number of these cases, *E. histolytica* is found (9.5%).

#### CONCLUSIONS

In carrying out parasite survey work it is necessary to examine a series of specimens and it is desirable to include a purge in the routine plus examination of specimens for at least two days after the purge.

Of men who have been prisoners of war in the Far East, a higher percentage carry pathogenic intestinal parasites (including *E. histolytica*) than do residents of Canada.

Dr. Eustace Morin, of Quebec, Dr. A. B. Walter and Dr. A. Branch, of Saint John, N.B., Dr. C. M. Harlow, of Halifax, gave invaluable assistance in the collecting of clinical and other data. Miss Patricia Oldham, B.Sc., Parasitologist, took part in the last half of the survey and her experienced assistance was an essential contribution to the completion of the survey.

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With all the advances made in the diagnosis and treatment of cancer in the last twenty-five years, it is a fact that the reduction of cancer mortality, potentially possible, has hardly begun. The primary reason for this failure is not due to inadequate therapeutic measures. The basic cause for the lack of improvement is the prolonged delay between the time when the patient has first symptoms and the time when definitive treatment begins. —J. E. Leach and G. F. Robbins, *J. Am. M. Ass.*, 135: 5, 1947.

## CASE REPORTS

### AVULSION FRACTURE OF THE BASE OF THE SECOND METACARPAL

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Avulsion fractures are relatively common in many anatomical areas in the realm of orthopaedics. These fractures produced chiefly by indirect violence are common to all of us and consist of the tearing away of a fragment of bone at the osseo-tendinous junction. The fracture to be described is unique in that I have never seen nor have I been able to locate a description of this type of fracture in this particular anatomical location.

On February 13 of this year, a husky white male of 29 years reported to me with a grossly swollen right wrist and hand. His story was that two days previously, he had been scuffling with a fellow workman and had received this painful injury. In the course of the scuffle he had struck his opponent on the shoulder with the back of his hand with considerable force and had felt a painful snap in his wrist. Shortly afterward, the dorsum of his hand and wrist became considerably swollen and function was seriously handicapped.

On examination, the back of the right hand and wrist were swollen and slightly ecchymotic. The range of mobility of the wrist joint was grossly restricted and the power of extension was practically nil. On palpation it was found that there were two points of maximal tenderness. One deep in the anatomical snuff box and the other over the lateral side of the base of the 2nd metacarpal. Clinically, a fracture of the scaphoid was suspected, and he was sent for radiographic examination.

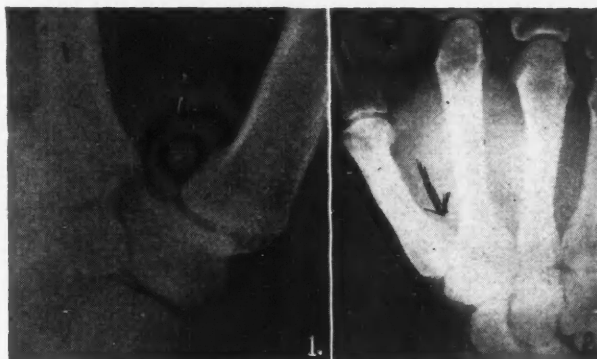


Fig. 1.—The deficiency on the lateral side of the base of the 2nd metacarpal is clearly shown. The avulsed fragment can be seen indistinctly superimposed on the carpus. Fig. 2.—The fragment is seen held securely in position by stainless steel wire.

Radiographs revealed the absence of the lateral tubercle of the base of the 2nd metacarpal from its usual position. This fragment of bone was then located  $\frac{3}{4}$  of an inch proximally overlying the mid carpus dorsally. The injury and its mechanism then became clear. It was concluded that the man had an avulsion fracture of the base of the 2nd metacarpal and that this had been produced by striking an immovable object while he was forcefully extending his shoulder, elbow and wrist simultaneously.



An open operation was done and the fracture site exposed by a linear incision along the lateral side of the 2nd metacarpal extending proximally one inch from its base. The extensor carpi radialis longus tendon and its attached avulsed fragment were isolated and drawn into position. The fragment was maintained in position by means of a stainless steel wire and the wrist immobilized in moderate extension by a plaster of paris cast. Radiographs revealing the fracture and its reduction are shown.

It will be recalled that there are four important extensors of the wrist and it is therefore easily understood that complete loss of extension was not apparent in the case. The extensors include the extensor carpi radialis longus and brevis, the extensor carpi ulnaris and the extensor digitorum tendons. The extensor digitorum tendons first extend the phalanges but by continued action they also aid in extending the wrist. In this particular case the extensor carpi radialis longus tendon, by violent action, avulsed its tubercle of insertion from the base of the 2nd metacarpal and distracted it proximally.

## RESUSCITATION BY CARDIAC MASSAGE

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J. D. C. MacDonald, M.D.

*Sarnia, Ont.*

During the past few years considerable attention has been focussed upon the procedure of cardiac massage in cases of impending death under anaesthesia. Leech<sup>1</sup> and Noble<sup>2</sup> in recent articles recommend it as an emergency measure in cardiac arrest. Easton,<sup>3</sup> MacLeod<sup>4</sup> and Grimshaw<sup>5</sup> report cases in which the manoeuvre was successful. Perhaps the greatest stimulus to interest in this subject followed Bailey's<sup>6</sup> report of a large series of cases. In this article two methods of performing cardiac massage are described. In the first method the right hand is placed beneath the diaphragm and ventricles of the heart and counter pressure is exerted by the left hand placed over the lower left costal margin. The second method, described by Nicholson consists of making a button hole incision behind the base of the xiphisternum between the attachment of the two sides of the diaphragm. The thumb of the right hand is thrust through the opening. The heart (within its pericardium) can then be compressed between the thumb above and the fingers below the diaphragm. In the following case the latter method was successfully employed.

F.S., a white male, aged 55, was admitted to St. Joseph's Hospital, Sarnia, on April 30, 1947. He gave a history of a duodenal ulcer unrelieved by medical therapy, over the previous 6 years. Apart from a localized epigastric soreness and moderate deafness physical findings were normal for a man of his age. A gastric series, done prior to admission, revealed an active duodenal ulcer crater. The blood pressure was 150 systolic, 80 diastolic and the pulse rate was 80. A complete blood count and smear examination, performed on admission, was within normal limits. The urinalysis was normal. Operation for trans-abdominal vagotomy and pyloroplasty or gastro-enterostomy was scheduled.

The patient was given nembutal gr. 1½ the night before operation and nembutal gr. 1½, morphine 1/6 with atropine gr. 1/150 intramuscularly at 7.15 a.m. the morning of his operation. Spinal puncture was performed with the patient in the left lateral position; 2% novocaine, to which had been added 15 mgm. of methedrine, was used as a local anaesthetic; 16 c.c. of 1/1,500 nupercaine was injected into the spinal canal without barbotage. The patient was then turned on his stomach and left in this position for seven minutes. At the end of this period he was turned on his back on the operating table. Anaesthesia was noted to extend as high as the nipple line. At this point, general anaesthesia was induced with 6 c.c. of a 5% solution of pentothal sodium. Cyclopropane anaesthesia was then established, using a Heidbrink gas machine. An intravenous infusion of 5% dextrose in saline was started and the operation was begun. At this point the patient's blood pressure was checked at 130/80, pulse rate, 90, and respiration 24.

On opening the abdomen it was found that a Levine tube, previously inserted in the patient's room, had not entered the cardiac end of the stomach. It was felt that this tube must be in position for successful performance of the operation so the anaesthetist was asked to push the tube down further. The mask was removed from the patient's face and an attempt was made to push the tube down which resulted in the tube curling up inside the patient's mouth. The tube was withdrawn and an unsuccessful attempt was made to insert a new tube. At this point, the patient began to recover from his inhalation anaesthetic so the mask was re-applied and cyclopropane anaesthesia was re-instituted carrying the patient to second plane of third stage. In order to maintain anaesthesia, while another attempt was made to pass the Levine tube, 3 c.c. of 5% pentothal solution was injected into the intravenous tubing. Using a laryngoscope and Magill forceps, and under direct vision, the Levine tube was passed down the oesophagus and was felt by the surgeon to enter the stomach. This procedure occupied approximately three minutes.

On removal of the laryngoscope the patient was seen to be markedly cyanosed. An oro-pharyngeal airway was inserted, the breathing bag filled with oxygen, and the mask re-applied to the patient's face. Respirations had ceased. Artificial respiration was performed for about thirty seconds by rhythmical compression of the breathing bag. At this point there was no change in the patient's colour and it was noted that pulsation of the temporal artery was absent, and the blood pressure could not be recorded. Simultaneously the surgeon reported the absence of pulsation in the aorta and also that he could feel no contraction of the heart by placing his hand on the under surface of the diaphragm. An attempt was then made to massage the heart through the diaphragm and at the same time one ampoule of coramine and one ampoule of adrenalin was injected into the intravenous tubing. Artificial respiration was being carried on by means of rhythmical compression of the breathing bag.

At the end of approximately two minutes no response of the heart had been noted so the abdominal incision was extended up past the xiphoid through the diaphragm and the pericardial sac was opened. The thumb of the right hand was then introduced into the pericardial sac and it became possible to grasp the apex of the heart, between the thumb and the fingers placed on the under

surface of the diaphragm. Massage of the heart was begun and at the end of about a minute to a minute and a half a faint flicker was felt within the heart. Massage was still continued; the faint flicker occurred more often until finally a definite contraction was felt. The contractions at the start were intermittent, irregular, and lacked force. Finally the contractions became very strong and forceful, regular and rapid. With increasing force the blood pressure rose to 160/90 and with this rise the superior epigastric arteries, which had been cut, began to bleed furiously. These were ligated. Respirations were resumed about two minutes after the heart started beating.

After a wait of five minutes the respirations were normal, the blood pressure was maintained at 160/90 and the pulse rate was regular at 90. Because of these findings it was decided to proceed with a posterior gastro enterostomy. Throughout this procedure the patient was given oxygen only. On closing the peritoneum he began to struggle, so 2 c.c. of 5% pentothal sodium was injected into the intravenous tubing. This caused a respiratory arrest of three minutes. His colour was kept good by pressure on the breathing bag and the pulse and blood pressure remained unchanged. He was returned to his room one hour and thirty-five minutes after the start of his anaesthetic in a satisfactory condition. His blood pressure was 130/70, pulse 100 and regular.

His condition for the next twenty-four hours was not particularly eventful. His blood pressure fell to 98/80 on two occasions but was restored to an average of 110/90 with cortate. For three days following his operation he appeared mentally confused and was made to understand with difficulty. His nurses reported that he would ask the same question repeatedly and that his memory was poor. This began to clear on the fourth and fifth days and from then on the patient improved rapidly. He was discharged to his home on the sixteenth postoperative day and his condition was considered good.

This patient was last seen in the office on August 25, 1947. He had returned to his normal work, that of a salesman. He had no complaints, no evidence of cardiac distress and was free of gastric symptoms.

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### LOCKED TWINS

J. Hans S. Geggie, B.A., M.D.

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A doctor hesitates to publish his failures, and yet possibly there is more to be learned from failures than from successes. Perhaps publication of the following failure will console, if not enlighten some other rural practitioner.

Locked twins is an uncommon condition, one in 90,000 deliveries. The *Queen Charlotte Textbook of Obstetrics* points out that, "the whole question should hardly arise with the exercise of that watchfulness on the part of the accoucheur which the parturient woman has a right to expect". Nothing is suggested to correct the condition in advance of the emergency. That cure-all (and precursor of future prob-

lems) Cesarean section, is a possible answer, given the necessary environment.

Mrs. W.S., aged 25, was seen on April 9, 1947. She had had four living healthy children, and six abortions. There was a history of twinning on both sides of the family. Social conditions were deplorable. Her last menstrual period was September 24, 1946. Weight 145 lb., blood pressure 130/80, pulse 78, urinalysis negative. Abdominal examination showed the uterus at the level of the xiphoid, and a round firm mass in left upper quadrant. Abdomen was tense. No small parts found; presenting part fixed. Rectal examination: vertex engaged. Cervix thinned out and 2 fingers dilated. Diagnosis: twins or hydramnios.

April 26, 1830 hours: pains every 2½ minutes. Vertex presenting in mid pelvis. Cervix fully dilated? Hot S.S. enema.

1915 hours.—Membranes bulging through the vulva. Snipped with toothed forceps. Nembutal gr. 3.75 intravenously.

1920 hours.—Breech (footling) at vulva. Descended slowly to the angles of the scapulae when descent ceased. Arms extracted, during which manœuvre a head was found posterior in the pelvis.

Deep chloroform anaesthesia and an attempt made to disengage vertex presentation, failed. Decapitation of breech presentation. Quick, easy forceps delivery of vertex. Although cardiac impulse was present prolonged resuscitation including coramine, lobeline and contrast baths failed to establish respiration.

2030 hours.—Membranes bulging in vulva: pituitrin min. ii

2045 hours.—Severed head born spontaneously.

2050 hours.—Binovular placenta delivered spontaneously. Pituitrin ½ c.c. Uterus clamped down rapidly. Bleeding no more than is normal in normal deliveries. Mother's condition good.

The placenta were separate but adjoining at one point of the circumference. Umbilical cords inserted separately in centres of respective placenta.

The twins: breech presentation was a girl, weight 5¼ lb.; vertex, a boy, weight 5¾ lb. Both babies were normal on gross examination.

The patient received morphine gr. ¼ hypodermically, and ergot aseptic 1 c.c. intramuscularly. Post partum course was uneventful. No rise in temperature.

#### DISCUSSION

There are lessons to be learned from this case. Few are applicable under the environmental conditions as they existed. I am reminded of the distraught candidate for an oral examination. He had many answers, but no correct ones. Finally he hissed, "I'd call you in, Sir!" Even this is not an answer. The eminent obstetrician who so castigates me in *Queen Charlotte's Textbook* might have felt rather helpless under the conditions which existed. In fact if he could not have paddled a canoe across a swollen, maddened river, he would not even have arrived on the scene!

Environmental conditions dictated the surgical management of this case. The operation was done under less than antiseptic conditions. Asepsis in rural obstetrics is impossible of attainment. Where the whole conduct of labour must be managed by the doctor alone, gloves, gowns, drapes, masks, etc., quickly become con-



taminated; and in an effort to prevent this, one finds oneself standing helplessly in a corner with arms at approved angles while the patient carries on as best she can. Our aim in rural obstetrics can only be antisepsis. Good antisepsis is better than contaminated asepsis. My midwives I train merely to keep away, and I relegate them to the north end of the patient. Most are capable of giving chloroform under supervision. Soap, water and alcohol is sufficient scrub-up for uncomplicated cases, and can be repeated as often as contamination occurs. Iodine can be added when pelvic examinations or other surgical interference is necessary. Liberal amounts of lysol provide a Listerian atmosphere!

What are the results of my heresy? In 154 unselected deliveries, including forceps, internal versions, etc., I have had one post partum infection. This occurred in a placenta prævia on the third day following an internal version and extraction. Her temperature reached 101  $\frac{4}{5}$ ° F., and quickly subsided after a large dose of penicillin intramuscularly, calcium penicillin and sulfadiazine by mouth, and ergotin gr. iii b.i.d. orally. In fact, contrary to university teaching, home obstetrics is not fraught with post partum temperatures. To the criticism that my follow-up care is not sufficient to display minor or major infections, I have to admit this is so. Nevertheless, the figures stand, with no green plots as a backdrop.

The drugs used in the above case are also open to criticism. Intravenous nembutal is not new in obstetrics, but evidently has been largely superseded by newer, less effective drugs which permit of telephone prescription. Nembutal, given intravenously is my preferred sedation in multipara. It provides an often much-needed relaxation for 10 to 15 minutes. Progress of labour is more rapid after its use. Comfortable sleep between pains is an almost constant feature. Excitement is minimal. A smaller amount of terminal anaesthetic is necessary, I have seen no troublesome asphyxia in the child resulting from it, as the effects are almost completely dissipated in  $\frac{1}{2}$  to  $\frac{3}{4}$  hour. I fear no post partum hæmorrhage as a result of its use. I use it routinely.

Chloroform is the smoothest, the safest and the most effective anaesthetic available to a general practitioner in rural Canada. There are precautions to be observed. It is not poured

like ether as I have seen it used in hospitals. It is not used for prolonged anaesthesia—ten or fifteen minutes is adequate for most obstetric uses where third stage anaesthesia is necessary. Possibly the prolonged use of chloroform anaesthesia and the earlier injection of nembutal may have jeopardized the life of the vertex presentation in the above case. However, there is not much room left in a pelvis for an umbilical cord when two large babies are engaged simultaneously.

The use of pituitrin in the above case is not too far out of line. I use it frequently, however, during the second, and even the first stage of labour. Some prerequisites are necessary. The head must be engaged, and the cervix at least two fingers dilated by rectal examination. The chloroform drop bottle and mask must be at hand. The first dose must not be more than one minim of pitocin, 10 international units to the c.c. It can be repeated at half-hourly intervals.

Finally, constant bedside attendance by the doctor is necessary for the safe and effective use of any of these drugs. I have spent as long as sixteen hours with one patient, though in these cases frequently storms and bad winter roads help to restrain my impatience to be home. It is unpleasant to fight one's way home over winter roads only to have to turn about and fight the elements all the way back again.

## PALINDROMIC RHEUMATISM

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The first case of palindromic rheumatism was noted by Hench in 1928, and published with a series of other cases as a "new" disease by Hench and Rosenberg in 1941. It is apparently a rather rare affection of the joints and par-articular tissues: at the Mayo Clinic five or six cases were observed yearly amongst the 4,000 to 4,500 cases of articular and muscular diseases of all types seen yearly by the Clinic's consultants on diseases of the joints. As in all "new" diseases the rate of recognition, and with it the rate of apparent incidence, will probably increase as time goes on. It seems to be worth while to add the present case to the small series of already published records.

Miss A.L., was seen first with relevant symptoms in November, 1945, at the age of 18. Her complaints at that time were swelling and tenderness of the right



wrist and both ankle joints. As part of her occupation she had handled heavy containers, and thought that she had sprained her wrist; the swelling of her ankles she noticed subsequently after a dance. At the time of the examination there was some slight puffiness of the right wrist; both ankle joints were noticeably swollen; there was non-pitting oedema and a bluish-red discoloration, especially on the anterior aspect of both joints. Both wrist and ankle joints were moderately tender. Otherwise, a physical examination did not reveal any abnormality. The temperature was normal, so was also the sedimentation rate (2 mm. in one hour, Westregren).

Her past history was entirely negative, in early childhood she had had varicella and measles, underwent a tonsillectomy and adenectomy in 1930, and again an adenectomy in 1943. There was nothing suggestive of allergy in her personal history. Emotionally she was somewhat unstable, and had a family background of very considerable emotional instability both on the paternal and maternal side. Her mother had suffered from seasonal asthma for many years, but repeated thorough investigation had never given a satisfactory or unequivocal result as to the nature of the responsible allergen.

The patient was advised to keep a week's bedrest, and the swelling of wrist and ankles subsided quickly.

After being up and about for a few days she presented herself again with swelling of the ankles. There was only slight pain, but considerable tenderness to touch. Again, physical examination revealed nothing, and the sedimentation rate was, again, normal. The patient kept another two weeks' bedrest, with the same immediate good result as before, only to be followed by recurrence of swelling and tenderness of the ankles as soon as she was ambulatory again. A careful search for the possible cause and nature of the rather puzzling condition was now made. As before, a thorough physical examination was negative with exception of the already described changes in the joints; the temperature stayed consistently normal; repeated sedimentation rates were entirely within normal limits; Mantoux and blood Wassermann test negative; blood and urine culture no growth; x-ray films of all teeth, the sinuses, chest, and affected joints normal. Blood count: 5,020,000 erythrocytes, Hbg. 13.5 gm. (photoelectrically), total leucocytes 7,450. Differential count: unsegmented 2%, polymorphonuclears 42%, lymphocytes 48%, monocytes 5%, eosinophiles 2%, basophiles 1%. No abnormalities observed on red or white bloodcells or platelets.

With hesitation the condition was labelled tentatively as a case of "atypical rheumatism". The patient was advised to keep a prolonged period of bedrest, and to stay under observation for further developments. A consultant re-evaluated the x-ray films and agreed that they were normal; the laboratory tests were repeated with the same negative result, and in addition an agglutination test for brucella was found to be negative. The consultant discharged the patient with the diagnosis of rheumatic fever, but took pains to emphasize that the clinical picture offered was quite atypical, and that the constantly normal sedimentation rate did not fit very well the diagnosis of rheumatic fever. Bed rest for two months and salicylates were prescribed. On her way home from the consultant circumstances necessitated the patient to walk a considerable distance while the outside temperature was below zero; her ankles promptly became quite swollen, and there was a considerable amount of pain. Swelling and pain subsided again after bedrest, and after two months' stay in bed, during which period there were no symptoms whatsoever, the patient resumed again her activity without untoward result. In July, 1946, she underwent appendectomy for an acutely inflamed appendix, and with the exception of some quite pronounced psychosomatic complaints she made a quick and uneventful recovery.

In December, 1946, she presented herself again with swelling of the right ankle joint; there was some bright red mottling of the skin overlying the affected area; the sedimentation rate and temperature were normal as ever. No medication was given, and the patient was advised to carry on with her usual activities. The swelling subsided within one week, and did not recur.

It was felt that this case offered something of a challenge as to diagnosis, and that its disposal as "atypical rheumatism" was quite unsatisfactory. It was, figuratively speaking, filed away in the mental compartment for undiagnosed and interesting cases.

While going over some current literature the recent case report of Hopkins and Richmond<sup>1</sup> was encountered, and it was at once connected with the above case. It seemed to offer a satisfactory solution to the diagnostic puzzle, and further reference to the original publications of Hench and Rosenberg and other papers quoted by Hopkins and Richmond confirmed the diagnosis of palindromic rheumatism beyond doubt.

The present case does not offer any further clue to the rather obscure etiology of palindromic rheumatism, nor does it deviate much from standard pattern. The normal sedimentation rate, the relative lymphocytosis, the beneficial influence of rest, the absence of radiological changes in the joints, also the psychosomatic component and the history of familial allergy have been described in previous cases. The rather outspoken seasonal incidence of attacks in our case is somewhat unusual. The cutaneous eruptions observed by us do not fit into the picture of palindromic rheumatism, but would rather make one think of angioneural arthrosis. However the whole question complex of angioneural arthrosis (Solis-Cohen) and allergic rheumatism (Kahlmeter) versus palindromic rheumatism seems to be so obscure and controversial, that it seems almost impossible for the non-rheumatologist to approach this problem at all.\*

A therapeutic attempt with pyribenzamine or benadryl may be of advantage in similar cases, as there seems to be at least an allergic component in many of these cases.

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\* Just before sending this paper to print (June, 1947) the patient reported by letter that she has had another attack of swollen and painful ankles.

## RECURRENT MASSIVE EPISTAXIS CONTROLLED BY LIGATURE OF THE EXTERNAL CAROTID ARTERY

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On the evening of May 12, 1947, I was called to the home of a patient who gave the history of having had recurring nose-bleeds during the past 48 hours. His nose was bleeding very profusely when I arrived. It was apparent that bleeding was from the left nostril in its superior region. I immediately packed the anterior naris and took him to the office. This controlled the hæmorrhage for about half an hour when bleeding recurred. Repeated packings were done, and after each, bleeding occurred through the pack. This went on until the patient had a massive hæmorrhage between changing packs and his condition became alarming from shock and semi-consciousness. I then was forced to accept that this was no ordinary type of nose-bleed and that more extensive emergency measures would have to be taken.

The patient was then removed to hospital by ambulance and Dr. Jacques Hebert, local oto-laryngologist, was called in consultation. The latter removed the blood-soaked packs and endeavoured to ascertain the cause and site of the bleeding. It was impossible to examine the nares or naso-pharynx for blood poured from both.

Packing the nose was made difficult because of a badly deviated septum to the affected left side. Nevertheless both nares were packed tightly against the floor and walls of the septum and a large postero-nasal tampon was inserted. A transfusion was given. The hæmorrhage was controlled for about 24 hours when profuse bleeding again recurred pushing out the tampon. Under sodium pentothal anaesthesia a further effort was then made to insert a pack to halt the hæmorrhage but bleeding forced itself through each successive pack and tampon. Oxy-cellulose was used but without effect.

The patient's condition now had become desperate even in spite of repeated transfusions. It was felt that if something more radical and more effective was not done soon he would die. Faced with this emergency I accepted the decision to tie off the external carotid artery on the left side. Under local anaesthesia an incision was made along the anterior margin of the left sterno-mastoid muscle. The external carotid artery was identified and tied in its continuity with three zytor ligatures between the superior thyroid and lingual branches. The patient was given whole blood throughout and after the operation. The pack was left in his nose for another 48 hours. At the end of this time when it was removed there was slight bleeding. A new pack and post-nasal tampon were re-inserted after the removal of which he has had no further bleeding. The total amount of blood lost after the ligature of the external carotid was about 40 to 50 c.c.

This patient was a robust, well-developed man, weighing 200 pounds, and in his early fifties. For some time he had been known to have hypertension. His pressure ranged between 200 and 220 systolic and 120 diastolic during the period he was bleeding and this in spite of his having lost about two quarts of blood. Of course he received about half of this quantity in transfusions. His bleeding, coagulation and prothrombin times were all normal and there was no evidence of any blood

dyscrasia. He had no nasal or throat infection to account for the continued hæmorrhage. The only explanation for the bleeding was that he had done a few days before hard, physical labour in a dusty office which he was not in the habit of doing. This may have increased his blood pressure and caused dryness and irritation in his nose sufficient to cause an erosion of an artery.

From the nature of the hæmorrhage one would conclude that the offender was the spheno-palatine artery on the left side with possibly a collateral branch from the ethmoidal, a branch of the ophthalmic artery.

This case is being presented with the object of showing that we cannot always regard nose-bleeds lightly and dispose of them by instructing the patient, perhaps by telephone, to put a clothespin on his nose, or apply cold cloths to the back of his neck. On the contrary epistaxis may be serious or dangerous to life as this one might have been if the external carotid artery had not been tied off.

I am deeply indebted to Dr. Jacques Hebert, oto-laryngologist, Rouyn, Que., who did all the nasal packings and worked so hard and zealously with me, after I brought the patient to hospital; to Dr. J. J. O'Reilly, Kirkland Lake, Ont. who was good enough to come to remove the final nasal pack with us and examine the patient about a week after operation, and last but not least, Dr. W. J. McNally, Montreal, for very valuable information by telephone.

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Psychiatry will make greater strides at that moment when it admits a moral as well as a mechanistic universe and begins to see that the denial of guilt is the greatest cause of morbidity in certain types of patients; that the self centered are always the self disrupted; that excessive self expression is self depression, and that what religion calls a sinner is in the psychiatric order a man who is a problem to himself; that the flight from life today through alcoholism, opiates and noise is an indication that no man can live with himself when he has lost all respect for self. . . .—Monsignor F. J. Sheen, *J. Am. M. Ass.*, 134: 1478, 1947.



## SPECIAL ARTICLE

### THE EVOLUTION OF THE MEDICAL FILM IN BRITAIN

Brian Stanford, M.R.C.S., D.M.R., F.R.P.S.

[This article appeared in "Documentary News Letter" (January-February, Vol. 6, No. 55, 1947) and was prepared for re-publication by the Medical Committee of the Canadian Scientific Film Association. It is to be noted that a considerable degree of parallelism exists between the status of medical film activity in Canada and Great Britain.]

As early as 1897 use was made of moving pictures to analyze gait defects but it was not until the advent of the 16 mm. film width in the early 1920's that medicine again looked at this medium and tried to use it for itself. Broadly speaking, two groups of practitioners became enthusiastic supporters of this new medium: the surgeon who wished to demonstrate repeatedly and at ease techniques which he performed only rarely, and the teacher of physiology who preferred the certainty of a film demonstration of an experiment to the vagaries of his biologic material for a demonstration.

Now these two classes, who make films for much the same basic reason, do so in different circumstances; for the physiologist can take surgical risks, can neglect the finer shades of aseptic technique, can repeat the experiment until an adequate record is made, and can personally supervise the cameraman. Not so the surgeon; he must place the safety of his patient before everything else, and he must give his undivided attention to the operation, leaving it to somebody else to make the film. And so we have today a number of amateur films which show physiological experiments crudely (in terms of photography) but satisfactorily in terms of teaching; while the corresponding amateur surgical films are in the majority of cases worthless for teaching purposes simply because the cameraman did not know what he was recording—what was significant and what he could leave out.

Physiologists, we have seen, bought their cameras and their film, made their records, and were content. Surgeons bought their camera and their film, were unable to make the record themselves, were discontented with the results other men made for them with their apparatus, and so turned to Messrs Kodak, who had supplied their equipment, for help. In 1929 the Kodak Medical Film Unit was established to make photographic records for surgeons. This pioneer unit did valuable work and made a large number of films. But it suffered from the lack of a medical man on the staff; the records were all made by photographers who learnt medicine as they went along, who were ignorant of what they were wanted to photograph, but who were assumed by the surgeon to know their job. Effective liaison between surgeon

and cameraman was rare, and the records they made are mostly poor quality; the area of interest in the picture is usually too small to show adequate detail, for the cameramen, feeling ill at ease in an operating theatre, preferred to hold their cameras in their hands than to place them rigidly on a tripod, and were therefore precluded from using long focus lenses; for the same reason the pictures are often out of focus, and continuity further destroyed by the film being made from a number of different angles, selected at random. Nevertheless, with purchases from other countries, the Kodak Medical Film Library grew until it is now the largest specialized medical collection in the country, and by the early 1930's substandard (16 mm.) cinematography was sufficiently widespread for several drug houses to found small libraries of films which they loaned out to medical meetings, often supplying a lecturer as well.

In 1933 the League of Nations Health Organization, at the suggestion of the International Institute of Educational Cinematography (formed at the suggestion of the Italian Government in 1928) decided to prepare an international catalogue of films. Great Britain, a participant member of the International Institute, went ahead with this work, and in 1936 the British Film Institute published its first catalogue of medical films, with a supplement issued in 1938. Unfortunately, the rise of Fascism prevented the full program of the International Institute from maturing, but this B.F.I. catalogue remained until very recently the only available catalogue listing films held by individuals or small groups in Britain.

The Royal Society of Medicine acquired 16 mm. projectors in 1930; and by now it was becoming fashionable to illustrate an address to a medical audience with films. Looked at today they appear to have been made, one cannot help thinking, to show surgical skill almost as often as to demonstrate techniques. For instance, there now exist at least fourteen films illustrating the operation for Cesarean section, not one of which shows sufficient detail for training a student. It is a spectacular operation with an obvious return for one's work; and was probably chosen in many instances as a trial by a surgeon to see what cinema could do, but the results were certainly discouraging. Yet this experimentation was not without value; lunch-table talk must have roused the interest of the physician, for neurologists were quick to see the value of this medium for teaching their students.

The films they made were often crude, but were better than those made by the surgeons, for once again they had time, could supervise the cameraman, and could take a repeat shot if the first was unsatisfactory. A number of useful films were made in this way, both at Edinburgh and Sheffield between 1930 and



1938. And now we are in the immediate pre-war years; colour film is becoming reliable, and students interested in photography are beginning to take an active interest in producing films for teaching themselves and their colleagues. Experimental units at Ashford and Manchester, financed for the most part by a surgeon, staffed and equipped by the students themselves, are producing better films. They know what they are recording; theatre ritual and technique holds no terrors for them; they have discussed in detail just what they want to show, and coached the surgeon to make sure he shows it; and just as they are all set to produce valuable films, it is already 1939.

Now the whole picture alters. Film stock for amateurs is scarce, time scarcer, facilities nil; the amateur, just feeling his strength, is eclipsed, qualifies hurriedly, and is called-up. But in wartime the health of the nation is important. "Health" films—dealing with vitamins, crèches, canteen problems, first aid—are wanted to inform the public quickly and in an attractive manner of the facilities that are available to them. Professional film units are called in to make these films, and they find the subject interesting, and make good films. Almost overnight it becomes obvious that many, if not most, of the films previously made for medical training are obsolete. The British Council in 1943 finances at great expense two excellent films on medicine, carefully made by film experts collaborating closely with doctors. But the purpose of these films is not clear; beautifully made, they have little use, and the British Council instead of profiting by their experience and going ahead, makes little progress in this field. But Imperial Chemical Industries sees the value of good film technique coupled to good medicine, and in 1944 sponsors a series of eleven films on anæsthetic techniques, designed for medical students and nobody else. And now the page is finally turned: there can be no going back; medical films will in future be judged by the standard of these Realist Film Unit productions, until an even better series is made. The film profession has invaded medicine, and medicine has invaded film, and that is where we are today.

What will follow? Films of this type are expensive; very expensive by the old standards. A thirty-minute talkie will cost £5,000 at the very least. No individual can afford that, and no group exists to administer joint funds. Some co-ordinating scheme must be produced on a nation-wide basis.

And what of the amateurs, eclipsed in 1939? The indications are that they are coming back to pick up the threads where they left off, but greatly strengthened by the wide demand for films which this war has brought about. They used to be doubtful of themselves—films in teaching were an experiment—but the war experience has justified their enthusiasm, for

what soldier has not been taught complicated techniques by films, and don't they know it? And what is more, their opinion is backed by scientifically designed psychological testing experiments. A technique so useful for soldiers will be equally useful for students. But slapdash technique is dead; impromptu camera-pointing is gone for ever. Hospitals and universities are already officially supporting these small film units, run by enthusiasts who know their photography, their medicine, and their curriculum; units which are going to make films to meet the local demand, and send copies to other centres if asked.

But so far we have only considered production; the film when finished must be made available as widely as possible, for the hospital-unit film will often cost £50 to £250 even if the time of the staff involved is left out of account, and it will be impossible as well as wasteful for any one centre to make itself all the films it needs. A centralized catalogue is necessary, giving details of all the films already existing, and kept constantly up to date as new films are made; this work is now being undertaken by the Royal Society of Medicine in conjunction with the Scientific Film Association, and publication is expected to begin early in 1947. A central library is needed to house the finished films, for it will be immediately obvious that it is more convenient to borrow films from a central point than from a number of scattered places. But that, a matter of convenience is of no great importance; what is far more important is that the film, both before and after projection, should be examined and, when necessary, cleaned or repaired; for if the film is not properly looked after, its life is shortened and it may break during projection, which causes much annoyance to the audience. This "film maintenance" is a skilled job requiring specially trained staff and machinery, and the expense of keeping up such a staff is not justified in a small library. So it is in the interest of all small libraries to pool resources to maintain an adequate inspection service for their films.

So much for distribution. Now we come to planning. First, a survey of the films available must be made; this is being done at the Royal Society of Medicine as has already been mentioned. Next, they must be reviewed and their teaching value assessed; this task is already being undertaken by the Scientific Film Association. After that, an attempt must be made to discover what subjects teachers most desire to be covered by films; this has been done by the Medical Committee of the Scientific Film Association, whose report has been published. Lastly, a system must be brought into being to ensure that, wherever possible, no two units are making a film of the same subject without being aware of each other's activities; this problem also is being tackled by the Medical

Committee of the Scientific Film Association who invite units contemplating making films to notify them well in advance; when two units are found to be overlapping on the same subject they are, if they agree to it, notified of each other's activities and so enabled to co-ordinate their production scheme to the benefit of both.

That, very briefly, is the history of the medical teaching film in Great Britain. It now remains to see how this experience compares with that in other branches of teaching and learning.

It can be said immediately that our experience is not unique. Film as a method of teaching is in demand in all walks of life. It seems certain that the use of the film for teaching soldiers, fireguards, dockers and aeroplane builders in the war years has shown both teacher and pupil that here is a powerful technique. But it is equally certain that, whether the war experience has intensified this experience or not, it has certainly not caused it; the demand from the public before the war years was steadily rising; any factual film could be certain of enthusiastic reception from a rapidly increasing audience, and this demand is real and spontaneous to the extent that in spite of reaction from possibly a majority of teachers, the use of film in schools is now talked of as an accomplished fact, awaiting only the manufacture of sufficient projectors. There is, therefore, a wide field opening before us.

In medicine the only subject on which there is already a usable selection of films is anaesthesia, so we start with a virtually clean slate. We should make sure that in our enthusiasm we do not respond with a flood of worthless films, many duplicating each other. The demand is great, the resources small; we must use them to best advantage; we should avoid dictation; we should avoid the superplanners stifling our enthusiasm and initiative; we should above all ensure that unpopular or unproved techniques can still be published in film form; we must, in fact, maintain the "freedom of the cinema". But we should also be intelligent in our desire to maintain freedom; we must co-operate. We should pool resources, technical and financial, and we should make our results, the films, available to all who need them, regardless of whether they are a rich school or a poor one. We need a block government grant, administered by the teachers, to which is added the financial resources of smaller groups and from which any group may draw funds to finance a film program which a majority agree is needed. It seems reasonable to do this on a regional basis; for a given university to draw up a film program covering a broad subject area—say, elementary midwifery or medical (as opposed to surgical) disorders of infancy; another university would draw up a complementary program, *e.g.*, advanced midwifery or surgical disorders of infancy; the two univer-

sities would criticize each other's programs, eliminate overlap, add sections that the other requires, and then these integrated programs would be submitted for the approval of the financing body. They would be integrated on a broader basis into obstetrics and gynaecology, or paediatrics, and then the money allocated and production undertaken regionally by the university film unit for simple films or by a professional unit for the more complex films.

Such a scheme would prevent much overlap, duplication and worthless production; but it need not hold up production; for it is immediately obvious that films on some subjects are imperative, and for these the finance body could allocate a grant immediately.

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## CLINICAL and LABORATORY NOTES

### DURATION OF EFFECTIVE BLOOD LEVELS FOLLOWING ADMINISTRATION OF PENICILLIN IN PEANUT OIL AND BEESWAX

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and S. C. Buchanan,<sup>3</sup> B.A., B.S.A.

Montreal, Que.

The frequency with which penicillin in saline solution must be injected in order to maintain adequate blood levels leaves much to be desired from the standpoint of both the clinician and the patient. To reduce the rate of diffusion of penicillin into the blood stream and thereby prolong the period of effective penicillin concentration following a single injection, oil<sup>1, 2</sup> and oil and wax vehicles<sup>3, 4</sup> have been suggested. A preparation of penicillin in oil and beeswax (P.O.B.),\* as suggested by Romansky<sup>5</sup> but having 2% beeswax in place of the customary 4.8%, has been tested for its efficacy in maintaining therapeutic concentrations of penicillin in blood. The reduction in the beeswax content was made in an attempt to eliminate undesirable reactions that have been reported<sup>6, 7</sup> from 4.8% beeswax mixture. A combination of P.O.B. injection therapy and oral therapy has been studied also. The subjects were patients at the Montreal General Hospital.

#### METHODS AND MATERIALS

Each dose for injection contained 300,000 I.U. of penicillin in 1.5 ml. of peanut oil/2%

1. Chief Microbiologist, Ayerst, McKenna & Harrison Ltd., Montreal.
2. Resident Urologist, Montreal General Hospital.
3. Assistant Research Microbiologist, Ayerst, McKenna & Harrison Ltd., Montreal.

\* The penicillin in peanut oil and beeswax preparation and the oral tablets ("Cillenta") used in this study were manufactured and supplied by Ayerst, McKenna & Harrison Ltd., Montreal.



beeswax mixture. Injections were made into the gluteal muscle of patients, all of whom had normal kidney function. When intramuscular therapy alone was used injections were made at 9.00 a.m. and blood samples taken after 6, 12 and 24 hours. When oral administration was employed, an intramuscular injection was made at 8.00 p.m. and oral administration (100,000 units) was started at 8.00 a.m. and continued at 3 hour intervals until 5.00 p.m. Blood samples were taken 12, 18 and 24 hours after intramuscular injection. Schedules were arranged so that patients received their meals one-half hour following a tablet. No untoward local or systemic reactions to the use of the peanut-oil-beeswax mixture were observed in any of the patients during the course of the study.

Blood samples were assayed for penicillin by two methods: a serial dilution procedure in which *Streptococcus pyogenes* C203 was used as test organism. In both methods the penicillin sensitive strain of *Sarcina lutea*<sup>8</sup> was the test organisms. In both methods the penicillin standard was diluted in serum or in defibrinated plasma obtained from a zero hour sampling of the patient's blood. Dolkart, Dey and Schwemlein<sup>9</sup> have demonstrated the necessity of using serum as diluent for the standard in dilution assays and our own experience has substantiated their work. Likewise in the cup assay described below it has been found essential to use the same diluent (defibrinated plasma) for standard and unknown. Sherwood and De Beer<sup>10</sup> have reported incomplete recoveries by a cup method when the standard was diluted in 0.11 M phosphate buffer. They obtained almost complete recoveries by replacement of cylinders with discs. We have found that the cylinders may be retained if the same diluent is used for the standard as for the unknown.

In the serial dilution assay method, aliquots of sterile blood serum (1.0 to 0.05 ml.) were added to sufficient broth (2.0 to 2.95 ml.) to bring the final volume in each tube to 3.0 ml. All tubes were inoculated with one loopful of a 3-hour subculture from an overnight (18 to 20 hour) culture of *S. pyogenes* C203 incubated at 37° C. Presence or absence of growth was observed after 18 hours at 37° C. The penicillin standard was made to an initial concentration of 0.3 Oxford units/ml. in serum and diluted as indicated above. Beef heart nitrate broth<sup>11</sup> was found to be more suitable than beef heart-brain infusion (Difco) medium as it allowed inhibition of the test organism at lower concentrations of penicillin (0.010 to 0.015 units/ml.).

In the cup assay procedure oxalated blood samples were centrifuged, and the plasma was defibrinated by the addition of 1 or 2 drops of CaCl<sub>2</sub> solution and by slow stirring with a glass rod. Similarly defibrinated plasma from penicillin-free blood was used to dilute the penicillin standard to concentrations of 0.030, 0.090, 0.270, 0.810, and 2.430 units/ml. As these levels of penicillin produce inhibition zones against the test organism, *S. lutea*, ranging from 12 to 45 mm. in diameter, large assay plates<sup>12</sup> were used in place of Petri plates. With these the standard and the unknown can be set up on the same plates. Replicates of each were prepared as with Petri plates. Plotting of the logarithms of standard concentrations against the zone diameters gave a straight line graph from which the potency of the unknown samples was read. As this graph includes a wide range in concentration, from 0.025 to over 3.0 units/ml., dilution of the unknown samples was unnecessary.

Some advantages of the cup-plate over the serial dilution assay are: (1) plasma may be obtained immediately, while 24 to 48 hours'

TABLE I.  
CONCENTRATION OF PENICILLIN IN HUMAN BLOOD FOLLOWING INTRAMUSCULAR INJECTION  
OF PENICILLIN P.O.B.

Patient	Concentration in serum units/ml. (dilution assay)			Patient	Concentration in plasma units/ml. (cup assay)		
	6 hrs.	12 hrs.	24 hrs.		6 hrs.	12 hrs.	24 hrs.
1	0.240	(<0.060)	(<0.060)	11	0.150	0.080	0.027
2	0.300	0.120	0.030	12	0.435	0.245	0.058*
3	0.300	0.038	0.075*	13	0.215	0.163	0.045*
4	1.125*	0.600*	0.056	14	0.378*	0.325*	0.050
5	0.225	0.200	0.037	15	1.460	0.058†	0.034
6	0.750*	0.150	0.050	16	0.530	0.029†	
7	0.112	(<0.056)	(<0.056)	17	0.400	0.410	0.123*
8	0.225	0.112*	0.075	18	0.271*	(<0.020)	(<0.020)
9	1.250	0.375	0.075	19	0.750	0.242	0.070
10	0.450	(<0.056)	0.075				
Number assayable	10	7	8		9	8	7
Average units/ml.	0.498	0.228	0.059		0.510	0.194	0.058

\* Checked by repeat assays.

† At 14 hours.



delay is required for serum extrusion; (2) asepsis is of relatively minor importance to the cup assay, but is essential to the dilution assay; (3) a smaller sample of blood is required; (4) dilution of unknown samples is generally not required; (5) routine operation is simpler; (6) sharper definition of blood penicillin levels is obtainable; (7) better reproducibility of results is obtained.

from 11 patients who received an initial 300,000 unit intramuscular injection of penicillin P.O.B., followed by 400,000 units by mouth in doses of 100,000 units at 3 hour intervals commencing 12 hours after injection. The serum and plasma values were found to check closely. Assayable levels were found in all but one of the 12 hour samples of plasma and in all of the 18 and 24 hour samples. By the serum assay the number

TABLE II.  
PENICILLIN CONCENTRATION IN BLOOD FOLLOWING INTRAMUSCULAR INJECTION AND ORAL ADMINISTRATION

Patient	Penicillin concentration, units/ml. in:					
	Serum			Plasma		
	12 hrs.	18 hrs.	24 hrs.	12 hrs.	18 hrs.	24 hrs.
20	(<0.030)	0.075	(<0.030)	(<0.020)	0.087	0.019
21	0.038	0.120	0.075	0.035	0.086*	0.059
22	0.113	0.113	0.113	0.091*	0.092*	0.074*
23	0.425*	0.232*	0.425*	0.360	0.199*	0.396*
24	0.060	(<0.060)	(<0.060)	0.069*	0.080*	0.034*
25	0.175*	(<0.060)	(<0.060)	0.218	0.036*	0.040*
26	0.200	0.150		0.197*	0.135*	
27	0.300*	0.200*	0.050	0.397*	0.275*	0.091*
28	0.750		0.450	0.687*	0.512*	0.430*
29	0.075	0.045	0.056	0.090*	0.022*	0.067*
30	0.600*		0.112*	0.653*		0.175*
Number assayable	10	7	7	10	10	10
Average units/ml.	0.274	0.134	0.183	0.280	0.152	0.139

\* Checked by repeat assays.

#### BLOOD LEVELS FOLLOWING INTRAMUSCULAR INJECTION OF PENICILLIN, P.O.B.

In Table I are set forth penicillin concentrations in blood at 6, 12 and 24 hours after injection of 300,000 units of penicillin in oil and 2% beeswax mixture. Assays were conducted on serum from 10 patients, and on defibrinated plasma from 9 patients. In each series 80% or more of the patients had assayable levels 24 hours after injection. Average concentration of penicillin for the 3 periods showed good correspondence by both procedures. The dilution method gave average values of 0.498, 0.228, and 0.059 units/ml. for the 6, 12 and 24 hours periods, respectively, while the corresponding figures by the cup assay were 0.510, 0.194 and 0.058 units/ml.

The penicillin blood level for this period, 0.058 units/ml. represents twice the penicillin concentration (0.030 units/ml.) usually regarded necessary for most penicillin-sensitive organisms.

#### INTRAMUSCULAR INJECTION OF PENICILLIN P.O.B. COMBINED WITH ORAL THERAPY

In case of severe infection or where the infecting agent is more resistant to penicillin, higher blood levels of penicillin are desirable. As a possible means of meeting this need, oral therapy was combined with intramuscular injection. In Table II are presented the data

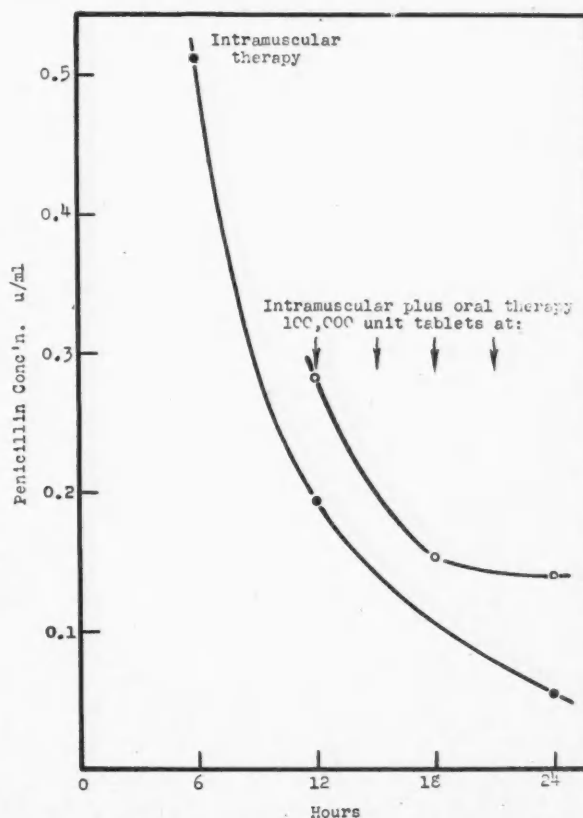


Fig. 1.—Human blood levels of penicillin following injection of 300,000 I.U. P.O.B. and following injection combined with oral therapy.

of assayable levels found at 18 and 24 hours was not quite as high.

In Fig. 1 a graphic comparison is made of the intramuscular therapy and the intramuscular plus oral therapy. The effect of the superposition of the oral therapy on the injected dose is seen by the levelling of the penicillin concentration in the blood after 18 hours at about 0.150 u/ml. Thus the penicillin P.O.B. injection produced an average concentration of about 0.06 u/ml. at 24 hours (or twice the effective therapeutic concentration), whereas the combination of injection with oral therapy produced an average concentration of about 0.14 u/ml. (or over 4 times the effective therapeutic concentration).

#### SUMMARY

1. Intramuscular injection of penicillin in peanut oil/2% beeswax and similar intramuscular injection followed by oral penicillin administration were employed to determine duration of maintenance of therapeutic penicillin concentrations in the blood.

2. Assays were conducted by a serial dilution method using blood serum, and by a cup-plate method using defibrinated plasma. The latter had several advantages over the dilution method from the standpoints of accurate determination of penicillin levels and ease of operation.

3. Intramuscular injection of 300,000 units gave assayable penicillin levels at 24 hours in 80% of 19 subjects. The average penicillin concentration at this time was 0.058 units/ml., or twice the effective therapeutic level.

4. Intramuscular injection of 300,000 units followed at 12, 15, 18, and 21 hours by oral administration of 100,000 units per dose, assayable penicillin levels were found in all of 10 subjects when the cup assay method was used. The average 24-hour level was 0.139 units/ml., or four times the effective therapeutic level.

5. Combination of oral with intramuscular therapy maintained higher penicillin blood levels than were attained by intramuscular injection alone.

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#### VENEREAL DISEASE AS A MEDICAL SYMPTOM OF SOCIAL PROBLEMS

In the opinion of Dr. Gordon Bates the venereal diseases are the medical symptoms of a social problem, and failure to control the VD rates rests very largely on the fact that in the past, while medical facilities aimed at their control have been developed, sufficient consideration has not been given to the social factors involved. Little progress has been made and VD clinics are still crowded despite the fact that means of cure are effective and popular education concerning the diseases is widespread.

"With the advent of rapid cure by penicillin, the infected patient cured of gonorrhoea in a day or two, in the absence of social and moral controls, is prone to promptly go out and get infected again," Dr. Bates said. "In my own clinic in Toronto General Hospital, a recent survey of 150 new cases of gonorrhoea revealed 59 were repeaters—individuals who had recently been cured. In some cases there had been as many as six infections during the last year."

Dr. Bates suggested that social surveys, using a carefully planned social case sheet, should be adopted for getting information concerning related problems, other than medical.

"Some health officers will express the opinion that their duty is purely medical, and that the social, moral and economic approach is none of their business," he said. "I suggest that the very fact that venereal disease rates are not decreasing immediately throws on the health officers a responsibility in all these different fields. Aside from everything else the physician and the health officer certainly have responsibilities as citizens which should come first, as far more important than any restrictions which their own professional position seems to impose upon them."

"It is perfectly obvious that mere education as to facts of venereal disease and the provision of treatment facilities will not control a problem which is social in origin."

—Health News Service

"... Here, then, is an affirmative answer to the question: Do we have the natural resources to meet world food goals by 1960? This answer is a challenge to all men, not to scientists only, for it raises immediately an even more critical question: Can we mobilize these resources to produce the needed food? This question begs many answers, because it involves the whole field of human relationships. Science may discover and point the way, but it cannot dictate. The full measure of success in economic, social, and political action comes only with the will of the majority—not from the desires of one group. If the people of the world really have the determination to give battle to the problem of hunger, if they are willing to expend a small part of the energy and capital poured into World War II, only then can we see hope of victory."—Robert M. Salter, chief of the Bureau of Plant Industry, Soils, and Agricultural Engineering, U.S. Department of Agriculture, Beltsville, Maryland, *Science*, p. 533, May 23.

## THE CANADIAN MEDICAL ASSOCIATION

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### EDITORIAL

#### MEDICAL REGISTRATION IN CANADA

THE legal requirements for the right to practise medicine in Canada clearly reflect the extent to which each Province has maintained its independence in the sphere of medical education. The mere acquisition of a medical training carries with it no right to practise. Registration is necessary, and each Province retains the privilege of granting or withholding this, so far as its own territory is concerned. It was recognized from the earliest days of our Association that uniformity in registration throughout the Dominion would be highly desirable, and for many years our predecessors made earnest and repeated attempts to introduce some such uniformity. They never entirely succeeded. A valuable compromise was finally effected, one which in view of the difficulties of the problem conferred lasting fame on the man whose labours brought it about—Sir Thomas Roddick. But it still was a compromise. The Roddick Bill in 1912 brought into operation the Canada Medical Act, by which a central body, the Medical Council of Canada, was created. This body was given the power to hold examinations and keep a register. Those who passed these examinations were granted a Dominion license and registered for practice anywhere in Canada.

But this apparent uniformity was weakened by the fact that in order to take the Dominion Council examinations an enabling certificate from some one Province was required; and each Province reserves its right to refuse such certificates when it sees fit to do so. Even if an enabling certificate was issued by Province A, Province B could exercise its rights by refusing to recognize it and the Dominion license.

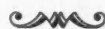
Two main factors affect the outlook of the Provinces in this matter. The first is the variability of standards of medical education. This was much more in evidence in the early years of our Association, when the older

Provinces led in standards of medical training. These standards are now uniform in Canada, but there still are criticisms of the readiness with which some Provinces will issue enabling certificates without the candidates having had sufficient intern training. Also, it seems that some Provinces are more ready than others to issue enabling certificates to medical men whose training has been taken outside of Canada.

The second factor is that of self-protection. In this respect the Province of Quebec has always led the way. It has its own problems in which the racial difference predominates. French universities in Quebec are providing a steady supply of medical men, practically all of whom remain in their Province. The admission to Quebec of practitioners trained in other countries is therefore very carefully watched.

These are some of the points to be borne in mind in considering the regulations which reasonably exist for those who wish to practise medicine in Canada. These requirements have been the subject of some critical comment in the press. It is known that many medical practitioners in Europe are turning their eyes to Canada. It is also known that in certain rural areas of Canada a shortage of doctors exists. The apparently obvious solution is to bring these people in. The acute shortage of doctors in Canada generally however is a thing of the past. A balance must be maintained between the large numbers of graduates in prospect from our universities and the amount of occupation available for them. That balance can easily be upset by the sudden introduction of numbers of new practitioners. And who is to regulate distribution so as to provide that they settle only where they are needed, or that they will not eventually gravitate to areas less in need of them?

As things are the Provinces are watching their own interests and there is no central body which has the power to take over the care of those interests, if indeed, it is at all likely that there will be one.





### THE SHORTAGE OF NURSES

SOME months ago (June, 1947) we drew attention to the problem of the shortage of nurses. According to a recent article in the *Canadian Hospital* (August, 1947) by Dr. Harvey Agnew, it is questionable whether there is any appreciation of the gravity of the situation except by those directly concerned with providing nursing services—administrators, doctors, and nursing schools. In Dr. Agnew's opinion, and his experience allows him to speak with insight, a major national calamity will develop unless something is done to solve this problem. No constructive plan has been put forward to improve matters. Everyone hopes that someone else will find a solution, but the fact remains that no permanent relief is being planned. It would be bad enough if conditions were to remain as they are. But the demand for nurses is so insistent and so certain to increase, that the prospects of satisfying it are poor indeed.

Where do all the nurses go? If the present output of the training schools had to meet only the needs of, say, fifteen years ago, there would be no difficulty. But within the last eight years we have passed through a tremendous national crisis, with developments and exactions of an overwhelming nature particularly in nursing. Public health, industry, D.V.A., are three major fields whose requirements are incessant and rapidly rising. The hospitals themselves have programs for building and increasing their accommodation, but it is safe to say that if this expansion could be accomplished overnight the magic would be in vain since nursing personnel would be unobtainable. The same obstacle is going to hamstring developments in public health, and if any form of health insurance comes into effect, with its cumulative demands on hospital service, it will be yet another instance of building without counting the cost. It is to be noted that none of the varied employers of graduate nurses such as industry, public health, D.V.A., T.C.A., etc., train any nurses for themselves. The burden of producing this highly skilled type of worker falls entirely on a few civilian hospitals. Dr. Agnew feels that the responsibility for solving the problem lies more with those who draw most heavily on the supply of nurses,

rather than with the nurses and hospitals themselves.

The most urgent need is for a comprehensive study of the whole matter. What is actually known at present of salary and working conditions, or of student enrolment? Is the nurse's labour in the hospital used to the most efficient and economical degree? Is there any wastage of nursing staff in such positions as public health, stewardesses, receptionists, demonstrators, etc? Should the system of nursing education be revised? Until these and other questions are thoroughly explored no sound planning can be carried out. The inquiry will call for expenditure of money, and the Joint Committee which has for some time been giving its attention to the matter has no source of revenue. The assistance of both governmental bodies and of industry is essential.

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### EDITORIAL COMMENTS

#### National Immunization Week

For five successive years the Health League of Canada has sponsored a national immunization week, beginning this year on October 5, to emphasize the necessity for continued attack on certain communicable diseases. These diseases are largely preventable. In smallpox of course success has been most complete, and all that is necessary in that respect now is constant vigilance to maintain the protection of vaccination. Next in the order of controllable disease is diphtheria, in which toxoid would probably attain as great success as smallpox vaccine has done, if widely enough used. Whooping cough vaccine is lowering the incidence and severity of the disease very encouragingly, but calls for much wider use. Scarlet fever too can be effective to a valuable degree.

The constant repetition of these facts is necessary both to maintain our ground and to make further advance. The toll of communicable disease in Canadian children is still too high. This immunization week is a valuable stimulus towards lowering it.

## MEDICAL ECONOMICS

### THE SIGNIFICANCE OF VOLUNTARY PREPAID MEDICAL SERVICE PLANS\*

Wallace Wilson, M.D.

Vancouver, B.C.

What exactly do we mean by "significance"? When I first considered the word, I realized that it was capable of several interpretations, but, in referring to Medical Service Plans, I do not intend to apply it in the sense in which it was used by an ancient writer when he remarked that the stars were significant but as a source of light, not very efficient. Rather will I discuss these plans under three other shades of meaning that can be given to this one word, "significance"—the *meaning of*, the *importance of* and the *consequences of* Voluntary Prepaid Medical Service Plans.

Let us first consider the *meaning of* these Voluntary Plans. For one thing, the rise of these plans represents a marked change in the arrangements by which people purchase or obtain medical care. Changes have occurred in the methods by which people obtain medical services ever since antiquity, but the tempo and extent of those changes have been greatly accelerated since the turn of the century. To what fundamental causes can we point as the driving forces that are at work altering the pattern of the provision of medical services?

Actually, the changes that apply, particularly to medical services, are but a small part of that great body of change that is taking place in the way of living, not only of the Canadian people, but of the whole world. It is no new phenomenon that today, mankind is searching and probing in an endeavour to find happiness and security with freedom from fear. But why have the efforts of all these people been so much greater and so much more purposeful during the last 25 years?

Part of the answer lies in the unstable and deplorable state in which the whole world finds itself politically, socially and morally; part in the tremendous strides made scientifically and economically. But a greater part of the answer is found in increased education. Nowadays, ordinary people have much more access to schools of learning; multitudes of good books are on library shelves and in book stalls, and more and more thinking people are reading them; numerous and varied study groups and adult educational schemes are available and there is present for the asking the educational side of radio. As a result of availing themselves of some or all of these educational advantages, a continuously increasing number of

people are becoming aware as never before of what modern civilization is capable of producing—and that includes medical services.

All of us in this room can hark back to the days of the horse and buggy doctor in Canada; to the time when the practice of medicine was carried on largely by the family doctor; to the time when, alone and unaided by confrère or State, he, in their own homes, looked after his patients literally from the cradle to the grave on a fee-when-he-could-get-it basis.

Today, all that is changed. The great and varied advances in medicine have placed full training and knowledge beyond the competence of any one man, and so the sound of the specialist reechoes in the land—or should we say cities—and he is heard of, not only within the confines of our own ranks, but from workshop to pub and from boudoir to cocktail bar. Our hospitals are bigger and better with their x-rays and laboratories, their B.M.R.'s and their E.C.G.'s, and, incidentally, the art of medicine is in some danger of being eclipsed by the science of the test tube and the film.

But, of course, these are all very real blessings of modern medicine and people hear and read about them, and from bitter experience know the cost thereof. So they are searching for ways and means, either through State aid or by the voluntary use of the insurance principle, to have made available to themselves the benefits and the protection as to costs of up-to-date medical care and hospitalization.

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2. This protection will greatly add to the sense of security amongst all participants.

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I have already made this statement once before, and I repeat it now. I feel sure that, as presently constituted, Voluntary Prepaid Medical Service Plans cannot, and will not in the future, provide the answer to complete medical care for all the people. The very presence of the word "voluntary" rules out such a possibility. On the other hand, complete co-operation between plans and government is entirely feasible. Under arrangement and as a first step, the State could pay into the plans the premiums of all those unable to pay their own way. A next step would be the provision by the Government of suitable physical plants or doctors' workshops in those areas now lacking them. This would mean an increase in the number of doctors going into those areas, with the practice of a better brand of medicine, and, in those same areas, there would be marked increase in the enrolments under the plans. If consultants and specialists were still lacking in certain districts, the plans, by arrangement, could do one of two things. (a) Provide a certain basic income for specialists to make it worth their while to settle in those districts, or, (b) with the agreement of the profession, hire full-time specialists and base them on the doctors' workshops.

The third step, if taken, would, of course, be the introduction by the State of compulsory health insurance to which everyone able to do so would be obliged to contribute, but still leaving the provision of medical services in the hands of the plans operated by the medical profession. I would say that in the event of any Province introducing compulsory contributory health insurance, the fate of the voluntary schemes operated by the profession will depend on the strength, efficiency and popularity of the plans themselves. If the profession can demonstrate that it can run plans in a well conducted business-like manner, with a sound, reasonably low overhead, and can, at the same time, provide a high grade service to contented beneficiaries, any government should be grateful to have the opportunity of saying "Carry on".

One more question, and it is an interesting and important one. Will one of the consequences of the spread and enlargement of voluntary plans be the raising of the general level of the standard of practice, and will another consequence be an improvement in the general health of the people as a whole? The introduction of doctors' workshops with diagnostic facilities and specialists' services into rural areas would certainly raise the standards



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Some of the listed objects of the projected Ontario Plan are:

1. To standardize diagnostic and therapeutic methods when deemed necessary or where possible.
2. To assist the Government in the Province of Ontario, upon request, in strengthening the health services.
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If those objects are achieved, and the plan at the same time goes all out to raise the standard of practice, it will break entirely new ground, will accomplish something that has never been accomplished before, and it will be a living example for all other plans to follow and emulate.

I would then say finally that all plans accomplishing such objectives would be very important; they would mean much to the public and the profession; no one could foretell the consequences of their operations to the health of the people but all would agree that they were both significant and efficient.

## MEN and BOOKS

SIR ALMROTH WRIGHT

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In the spring of this year there died within a few days of each other, both at the age of 86, two men who have been outstanding in British medicine — Sir Almroth Wright and Sir Frederick Gowland Hopkins. The excellent notices which have already appeared in the *British Medical Journal* (May 10 and 24, 1947) are full of both factual and personal detail.\* Sir Almroth is probably associated in most men's minds with his work on immunization, which began in 1896. It was just a little too soon for the application of his work in the Boer War with its many thousands of typhoid deaths. But by 1914 he and his colleagues were able to alter the course of history. It was calculated roughly that antityphoid inoculation directly saved hundreds of thousands of lives in that war. But in the opinion of some his greater strength lay in his effect on research in general and in his fresh and unconventional point of view. "Dignity is a mysterious gesture of the body designed to hide deficiencies of the mind" he would say. Perhaps it was his unorthodoxy which endeared him to Bernard Shaw who used Sir Almroth as one of his characters in "The Doctor's Dilemma". But Shaw only used one aspect of Wright's personality, the ruthlessly scientific: he had another more lovable side. And he was a remorseless worker. He said that he would like them to put on his tombstone a quotation from Emerson's essay on intellect: "God offers to every mind its choice between truth and repose" and then would add with a twitch of his eyebrows "Repose is the more fashionable". Sir Henry Dale has said:

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And Dr. John Freeman adds:

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### THE SHORTAGE OF NURSES

SOME months ago (June, 1947) we drew attention to the problem of the shortage of nurses. According to a recent article in the *Canadian Hospital* (August, 1947) by Dr. Harvey Agnew, it is questionable whether there is any appreciation of the gravity of the situation except by those directly concerned with providing nursing services—administrators, doctors, and nursing schools. In Dr. Agnew's opinion, and his experience allows him to speak with insight, a major national calamity will develop unless something is done to solve this problem. No constructive plan has been put forward to improve matters. Everyone hopes that someone else will find a solution, but the fact remains that no permanent relief is being planned. It would be bad enough if conditions were to remain as they are. But the demand for nurses is so insistent and so certain to increase, that the prospects of satisfying it are poor indeed.

Where do all the nurses go? If the present output of the training schools had to meet only the needs of, say, fifteen years ago, there would be no difficulty. But within the last eight years we have passed through a tremendous national crisis, with developments and exactions of an overwhelming nature particularly in nursing. Public health, industry, D.V.A., are three major fields whose requirements are incessant and rapidly rising. The hospitals themselves have programs for building and increasing their accommodation, but it is safe to say that if this expansion could be accomplished overnight the magic would be in vain since nursing personnel would be unobtainable. The same obstacle is going to hamstring developments in public health, and if any form of health insurance comes into effect, with its cumulative demands on hospital service, it will be yet another instance of building without counting the cost. It is to be noted that none of the varied employers of graduate nurses such as industry, public health, D.V.A., T.C.A., etc., train any nurses for themselves. The burden of producing this highly skilled type of worker falls entirely on a few civilian hospitals. Dr. Agnew feels that the responsibility for solving the problem lies more with those who draw most heavily on the supply of nurses,

rather than with the nurses and hospitals themselves.

The most urgent need is for a comprehensive study of the whole matter. What is actually known at present of salary and working conditions, or of student enrolment? Is the nurse's labour in the hospital used to the most efficient and economical degree? Is there any wastage of nursing staff in such positions as public health, stewardesses, receptionists, demonstrators, etc? Should the system of nursing education be revised? Until these and other questions are thoroughly explored no sound planning can be carried out. The inquiry will call for expenditure of money, and the Joint Committee which has for some time been giving its attention to the matter has no source of revenue. The assistance of both governmental bodies and of industry is essential.

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### EDITORIAL COMMENTS

#### National Immunization Week

For five successive years the Health League of Canada has sponsored a national immunization week, beginning this year on October 5, to emphasize the necessity for continued attack on certain communicable diseases. These diseases are largely preventable. In smallpox of course success has been most complete, and all that is necessary in that respect now is constant vigilance to maintain the protection of vaccination. Next in the order of controllable disease is diphtheria, in which toxoid would probably attain as great success as smallpox vaccine has done, if widely enough used. Whooping cough vaccine is lowering the incidence and severity of the disease very encouragingly, but calls for much wider use. Scarlet fever too can be effective to a valuable degree.

The constant repetition of these facts is necessary both to maintain our ground and to make further advance. The toll of communicable disease in Canadian children is still too high. This immunization week is a valuable stimulus towards lowering it.



## MEDICAL ECONOMICS

### THE SIGNIFICANCE OF VOLUNTARY PREPAID MEDICAL SERVICE PLANS\*

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a glass of benedictine—which I knew he loved. On the other hand, he took enormous pains to get exactly the colours he wanted in his beloved flower garden at Stoke Poges; for him that was *not* a voluptuary pleasure. He was chary of listening to music because it affected him too much, and made him 'give at the joints'. Yet he could hardly have enough of poetry, and Dante and Milton were his poets: during tedious motor journeys in the first great war he would quote Milton to himself from memory—his mouth silently muttering for an hour at a time."

Sir Frederick Hopkins had an equally long and full life. Unlike Sir Almroth he had no formal scientific education at all, and after school was placed in the insurance business. Before long however he persuaded his guardians to allow him to take up a scientific career, and was to go to Cambridge when it was decided by an uncle that he would learn more as an apprentice to a practising analytical chemist. Possibly this might not have been too much loss of time, but as a matter of fact he was used only as a junior laboratory assistant. He attended some lectures on chemistry, the only lectures on the subject he was ever to hear. He then gained a post as a salaried analyst, but at the end of six months his pay was a cheque for £40. He suggested to his employer that it might be framed and the suggestion was gravely agreed to. However, his progress from now on was more rapid. He graduated in medicine and began a clinical career and was on his way to a flourishing practice when Sir Michael Foster offered him a lectureship at Cambridge in chemical physiology, and this was the beginning of his life work. He was essentially an investigator and his interest in chemistry supported him through a period of difficulty in establishing his department. He had shown this investigative spirit even in his early days as an analytical chemist when he carried on work on butterfly pigments in his mother's scullery.

The part played by Sir Gowland in the development of biochemistry and his share in the work which led eventually to the discovery of vitamins, is well summarized by Sir Henry Dale.

"When Hopkins was at the beginning of his work the chemical study of the animal body and its products had become a mere branch of physiology, having some links of practical method with clinical medicine. Chiefly a chemistry of end-products, it had almost lost an earlier and short-lived attraction for 'organic' chemists and was not everywhere in great repute with physiologists. He had been conscious of the need to win respect for this 'chemical physiology', by the achievement of results to which chemists as well as biologists must give attention, before the advance towards the real objective could begin. Hopkins lived to see 'organic chemistry' returning, with rapidly growing interest and with immensely greater resources of method and theory, to its original objective of the structure and properties of the relatively stable end-products stored or excreted by animals and plants. He lived also to see the dynamic chemistry of intermediary metabolism, in the foundation and building of which his work and his influence had played such a great part, achieving recognition as the essential 'biochemistry'.

"On the way to this ultimate objective Hopkins's work had dealt with a number of apparently separate problems in vital chemistry, so that his career as a re-

search worker seems to fall into periods. In the first he was bringing to the point of publication the work on the pigments of the wings of certain butterflies and their relation to uric acid, begun so early but not published until 1895, when he was already 34 years of age. In his latest years he actually returned to this earliest of all his problems. To the same early period belongs his work on human purine metabolism, including the introduction of what remained for years the standard method for determining uric acid. Then came the period of protein and amino-acid chemistry, beginning with practical methods for crystallizing certain albumins in any required quantity, and culminating in the discovery and isolation of tryptophan. This latter led to the study of the necessity of individual amino-acids in a mammalian diet, and thus, apparently, to the recognition of the inadequacy, for growth and maintenance, of a diet in which the organic constituents—protein, fat, and carbohydrate—had been rigidly purified from traces of unknown factors. This fundamental step towards the recognition of the vitamins, now engaging the attention of such a large proportion of the world's



**The Discovery of Tryptophane**  
(Kindness of Dr. I. M. Rabinowitch, Montreal)

biochemists, was mentioned by Hopkins in a lecture as early as 1907, though circumstances delayed the publication of his detailed experimental evidence till 1912, when the 'accessory food factor' or 'vitamin' conception was already in the air. Hopkins gave the first clear demonstration that it was no defect of appetite or absorption but a fundamental failure of the metabolism to deal with the adequate quantities ingested and absorbed which created the deficiency of the pure diet, and that a relatively minute addition of fresh milk completely repaired the defect. Meanwhile, in 1906, he had published with the late Sir Walter Fletcher the results of the first experiments which he made directly on a problem of intermediary metabolism—the production of lactic acid from carbohydrate in active or in-



jured muscle, and its removal in the intact muscle by oxidation."

An investigator of great genius himself he possessed the additional virtue of inspiring others to take up various problems. He had the rare distinction of real humility of spirit.

We are fortunate to be able to reproduce the accompanying photograph of Sir Gowland and one of his pupils, Professor Sydney W. Cole, taken at the Biochemical Institute, Cambridge, in 1901, on the occasion of their first isolation of tryptophane. Sir Gowland is holding the specimen. H.E.M.

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## MEDICO-LEGAL

### CANADIAN MEDICAL PROTECTIVE ASSOCIATION REPORT OF COUNCIL FOR THE YEAR 1946-47

It seems trite to state that the work done by your Council this year has imposed a burden heavier than in any previous year, that has been said year after year—and has been true year after year. The rate of increase has been greater actually over the past few years because the membership of the Association has increased faster. Membership reached 2,400 in the first thirty-five years of the Association's growth, in the last ten years that figure has been doubled and the work to be done has kept pace.

Most interesting problems are presented by many of the cases. Reporting them to members is difficult. There are many threats which do not get to court so no decision is reached and discussion of some has to be deferred until the decision of a court has been rendered. One case, having been decided, illustrates an important point and is to be discussed.

One of our members, one night, received a request for a call from a patient's wife because the patient was thought to have indigestion. Our member did not make the call but did give the wife such advice as seemed applicable and told her he would phone early in the morning for a report. After phoning early in the morning the doctor visited the patient and found that the indigestion was coronary occlusion. The patient was sent to the hospital forthwith where he died two days later. The wife brought action against the doctor, claiming negligence on the ground that the phone advice had been incomplete and that a visit would have led to earlier recognition of the condition, earlier treatment and a different result. The case came to trial before a judge and jury and our member was acquitted of any neglect.

The issues raised by this single case are important enough to warrant a general discussion

of the responsibilities of physicians when requests for help are made.

A doctor may divide that part of the public seeking his help into three groups. To the first group, those who have not been and are not at the moment patients of his, he has no legal responsibility, he may accept such calls on him as they make and he is equally free to refuse. Morally the position is somewhat different, he would be a callous physician who refused help to a patient in an emergency if he were able to give it. But, and this is the important point, he is free to refuse. To the second group, those who have been his patients and look to him constantly for such help as they need, but who are not at the moment under treatment, the legal responsibility is the same though the moral responsibility is somewhat greater. Legally the doctor may refuse to see them or treat them. Morally he probably should not. If he has allowed them over a period of time to consider him as their medical adviser he should be willing to accept such reasonable calls as they make on him. To the third group, patients under care at the moment, the legal responsibility of the doctor is greatest. Unless he has been discharged from the case or has served notice that he wishes to be relieved of his duties he is bound legally to do whatever, in his judgment, is necessary for the patient. While this does not imply that a doctor must go every time a patient requests a visit it does mean he can be held responsible if it can be shown that harm resulted to the patient because he failed to go when an ordinarily careful man would have gone.

The telephone introduces complications. The majority of calls, almost all of them, come over the phone. Unless patients supply them spontaneously most doctors ask particulars of the illness for which they are called. With these it often can be decided a call is not necessary and that advice over the phone is sufficient. Often patients do not request a visit, they merely tell what they know of the condition and request phone advice. What is the legal position of the doctor who, having refused to make a call or merely in response to a request, gives advice over the phone? What is his legal responsibility?

As a basis for an answer it is necessary to recall the usual legal responsibility of the doctor for his advice. He must have preceded his advice by such examinations and investigation as would be done by a reasonably careful and skilful physician under the same circumstances. So with his responsibility for telephone advice. He must have been able to obtain sufficient information to allow him to arrive at a conclusion with reasonable certainty. If it can be shown that this information could not, reasonably, have been expected to be conveyed over the telephone, the doctor might be held guilty of negligence or malpractice. For his own protection then the prudent physician will consider himself as responsible for advice given over the phone as for advice under the usual circumstances.

There may be times therefore when the physician must, in self-protection, refuse to give telephone advice. If he has any doubts about the condition described, doubts which he thinks could be resolved by examination, he must insist that opportunity for the examination be provided and unless it is provided he should refuse advice. If a doctor is unable to visit a patient too ill to come to him he should refer the patient to a colleague. If the patient can but will not come to the doctor there should be a definite refusal to give advice in any case of doubt. Only if, as is true of many doctors, the doctor is alone in a large district and is unable by reason of previous commitments or physical inability to make a call could telephone advice in doubtful cases be justified. There it might be held that the doctor had done the best possible under the circumstances. In towns and cities it is obvious such justification for telephone advice in cases of doubt could never be expected.

Two things your council feels should be dealt with specifically in its report this year are the question of doctors who find themselves in legal trouble more than once and the question of payment to a doctor who assists another to defend himself.

#### REPETITION OF ERRORS

The Association recognizes that a doctor may be forced to defend himself legally when he is without fault. Some patients are litigious and looking for trouble. Some results are poor because the conditions being treated preclude good results and examples of this are well known to all doctors, fractures of such complexity and severity that complete restoration cannot be had, infections at a stage or of such severity that treatment is ineffective and many other similar things. The Association does recognize, though, that few, if any, cases arise when the doctor has been without fault, it may only have been his handling of the individual patient, an inaccurate or incomplete explanation of the condition, perhaps more commonly an explanation altogether too involved and verbose for the patient to follow. Such things happen to the most conscientious and competent man. Much commoner however and the type of case to be discussed is that arising from some negligence or malpractice in a legal sense.

Examples are so numerous it is difficult to choose typical ones. A doctor administered intravenously on two occasions a solution which caused most unusual reactions. Only after the second injection did he read the label on the ampoule to learn he had been giving histamine when he thought he was giving ouabain. A doctor examined a patient one September, decided she had either a cyst of one broad ligament or an ectopic pregnancy, was not allowed to operate until the following January when he proceeded, without further clinical or

laboratory examinations, and found a normal pregnancy!

If one such case justifies some doubt of the competence of the doctor, two allow no doubt. One must look askance at the work of a doctor who, one year, has threats against him on the ground of improper certification and the next year because part of a surgical needle is said to have been left in a wound. Should not the doctor who one year has a surgical wound break open and discharge a gauze sponge and two years later has a patient develop syphilis after transfusion from an untested donor re-consider his whole manner of practice? Or the doctor who in the same year has a patient die during an operation for which no consent had been signed and in another discovers a pregnancy at operation when, without adequate preliminary diagnostic work, a diagnosis of uterine fibroids had been made? Is it possible to reach any other conclusion than carelessness in the case of a doctor who one year hears of gauze recovered following a D & C and the next year has a burn occur during cautery after preoperative preparation with alcohol?

Because during the past year several names were recognized as having been under discussion previously a review of the Association files was undertaken. It was found that between 1936 and 1946 no less than twenty-four doctors had requested advice or assistance two, or in some cases three times. Until the present the Association has dealt with all its members on the assumption that any doctor needing assistance had done his best work and that some reasonable explanation of his failure would be demonstrated.

Much thought has been directed to this problem by the Council, without as yet, it must be admitted, having reached a conclusion. If the habit of presuming each doctor to have done his best is to die it seems likely to require a long struggle. The Association, in the past, has given advice and assistance, has arranged settlements and paid legal fees for these members. It has done these things with a strong feeling that the cases could not have arisen without fault on the part of the doctor. It feels further, and strongly, that when any physician is in trouble repeatedly he cannot be altogether blameless. It is remembered, too, that the funds to assist these careless members are collected from the whole membership, the vast majority of whom are careful, the vast majority of them go through a whole busy, professional life without even a threat being directed against them. While the by-laws authorize Council to "terminate the membership of any member whose conduct or membership is considered to be detrimental to the Association" Council is loath to exercise this power unless too many repeat cases occur or unless the membership as a whole expresses the wish to be protected against the careless prac-



titioners. Some idea of how strongly Council feels its obligation to members can be conveyed to you by the statement that in the history of the Association no member has been refused assistance unless he was in default when the cause of the complaint occurred or the case was criminal. This is a record the Council would like to maintain if it does not work an injustice to the majority of members whose work is careful.

#### ASSISTANCE OF ONE DOCTOR BY ANOTHER

The question of doctors accepting payment for assisting others to defend themselves has been discussed in previous reports but because it arose in two cases during the past year another short discussion seems wise. By way of preface to the discussion two pertinent by-laws may be quoted. By-law No. 9 charges each of us that "It shall be the duty of every member of the Association to aid in the defence of any action when undertaken by the Association." By-law No. 13 states that "Fees for special expert medical testimony will not be paid by the Association unless specifically authorized by the Council."

It is a recognized principle among doctors that no fee is charged another doctor for professional services. It is true that the medical care of a doctor or his dependents is the type of professional assistance most often required and rendered and therefore most often thought of. Surely the use of the professional knowledge to assist another doctor to defend himself in court is as truly professional service and therefore should be rendered as willingly and with as little thought of fee as the medical care.

One or two confusing factors deserve mention. The first is the position of the Association as the guiding influence in a doctor's defence. The Association is not and does not regard itself as an insurance company, it enters into no contract with its members that it will or will not give specified services in specific circumstances, it does not propose and does not try to benefit financially by the provision of its services. It is a mutual medical defence union. In other words, it is a central office through which all doctors who so desire may pay a small annual sum into a central fund which each doctor knows is available if he needs assistance when he is faced with legal expense, the whole maintained without profit to anyone. The basic conception of the Association held by its founders and its officers since its beginning is that of mutual aid among doctors rendered through their own organization. The Association does not make any contracts; it does not "hire" expert witnesses; it does not operate for profit; it simply acts for each doctor in the manner shown by experience to be the most helpful to the individual doctor, to medical men as a whole and to the profession. Therefore, because the Association happens to be assist-

ing, the relationship between the doctor being helped and the doctor giving the assistance is not changed in any way, such assistance is to the doctor not to the Association. And one doctor does not charge another for professional services.

About the assisting doctor's expenses the Association tries to act as it thinks its members should act. It tries to see that the actual costs of assistance are returned. The Association remembers that the best men are most likely to be wanted as experts, that the best men in any district are few and therefore may find themselves giving more of this kind of help than all the rest of the doctors put together. Also because they are the best men their time is most valuable. These things are taken into consideration in deciding what may properly be considered expenses which should be paid.

Another source of confusion is the frequent insistence of Counsel that the assisting doctor render an account for his services. The counsel retained by the Association invariably are those judged the most competent. They in turn choose as expert witnesses to assist in the defence the doctors they judge most competent and experienced as well as the most effective witnesses, doctors with whom in many cases counsel have been associated in the past and with whom they hope to be associated in the future. Counsel recognizes that valuable experts are not to be had cheaply and make an effort to see that they are paid adequately. They do so not only in ordinary legal cases but in cases where doctors acting as experts are assisting fellow practitioners. Presumably they will continue to do so and doctors must remember the ethical principle involved and refuse to render accounts to their fellow practitioners. It would be a sorry state of affairs if the medical profession should suddenly find its members charging each other for professional help that should be given generously.

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## SPECIAL CORRESPONDENCE

### The London Letter

(From our own correspondent)

#### THE BRITISH ASSOCIATION

Whatever other useful function it may subserve nowadays (a point on which opinion differs considerably), it is generally agreed that the annual meetings of the British Association for the Advancement of Science provide a useful forum for leading scientists to offer *ex cathedra* statements on the practical applications of science and to discuss what may be conveniently described as the politics of science.

The first full post-war meeting, held at Dundee last month, has been particularly useful in this way as it dealt primarily with the application to peace conditions of the many outstanding scientific advances of the 1939-45 war. The tone of the meetings was set at a high level by Sir Henry Dale in his presidential address on "Science in War and Peace". The two main topics of his address are particularly applicable to the sphere



of medicine. The first of these is the danger to science if the demand for quick results, so essential in time of war, is allowed to persist into the post-war era. Applied science is merely one aspect of research, and unless the necessity for fundamental research is fully appreciated, particularly by those in control of industry and governmental departments, the standard of our research departments is bound to fall. There are many in the medical profession who share Sir Henry Dale's fear that scientists "may find it difficult to shake off quickly the spendthrift habit in research, the policy of trading for quick returns which six years of war experience may so easily have fostered and may even have made congenial to many of us".

The other outstanding topic of the address was the potential danger to all the fundamental principles of intellectual freedom involved in the tendency for the atmosphere of secrecy, again so essential in time of war, to become a permanent feature of modern research. This is a problem which has already been referred to in this correspondence, and it is also one to which several leading scientists have referred during the last year.

#### THE INCIDENCE OF INDUSTRIAL NEUROSIS

Many interesting facts are brought out in an Industrial Health Research Board report on "The Incidence of Neurosis among Factory Workers" which has just been published. This is based upon a survey carried out between 1942 and 1944 in thirteen light or medium engineering factories. Over 3,000 workers were selected out of a total population of 30,000 employees. The incidence of disabling neurotic illness was found to be 10% (9.1% of the men and 13% of the women). A further 20% suffered from minor neurosis. Neurotic illness was responsible for one-quarter to one-third of all absence from work due to illness.

Among the various factors responsible for the incidence of neurosis, emphasis is placed upon the home conditions, the nature of the worker's job and the conditions of work. For instance, neurosis was found to be associated with excessively long hours, inadequate lighting, tasks which are boring or disliked and work requiring skill inappropriate to the worker's intelligence. Unsatisfactory human relationships inside the factory were also a fruitful source of neurotic illness.

One rather unexpected finding was that among the factors tending to decrease the incidence of neurosis was more than average normal domestic responsibilities, associated with less than 75 hours of individual duty weekly. Thus, the married women with full home duties experienced better health even though they had been more often absent from work.

The implications of this important report for peace-time conditions will require careful attention, but much thought will need be given to one of the suggestions: that "it may be less important to make jobs 'fool-proof' than to design them so that they will not be disliked, found boring, nor demand long periods of close attention to unvarying detail".

#### THE PROBLEM OF BURNS

Much attention is being attracted by a recent article in *The Lancet* by Dr. Leonard Colebrook, the director of the Medical Research Council's Burn Unit at the Accident Hospital, Birmingham. Dr. Colebrook has long been known for his brilliant work on this problem, and his unit at Birmingham is an outstanding feature of British hospitals. His article is a plea for the setting up of such units throughout the country when the new hospital service is introduced. That his premises are valid is shown by the figures he produces for the Birmingham unit. The death-rate among the 203 children, aged 0 to 12, treated during the last two years has been 3%, compared with 32% among the 100 children of the same age-group reported from the Toronto Children's Hospital in 1923. During 1945-46, 23 deaths occurred from burns and scalds, but only one death from scalding among the 120 children (aged 0 to 12 years) treated. Before the 1939-45 war such

deaths in children accounted for more than 30% of all deaths in the Registrar-General's reports.

Dr. Colebrook's suggestion is that such units should be established in one or more general hospitals in every large city and town in the country, and that all cases of burns and scalds should be admitted to such centres and not to any other hospital. In addition, he insists upon the necessity for all dressings of burns being carried out in specially ventilated dressing-rooms designed to avoid both air-borne and contact infection.

As some 1,200 people die of burns and scalds each year in England and Wales, the saving of life that would result from such an organization is evident. The fact that Dr. Colebrook is in the strong position of being able to provide ample and vivid confirmatory evidence of the value of his scheme may well ensure its ultimate adoption. No-one begrudges Birmingham its lead in this matter, but there is a growing consensus that it is time other cities attempted to emulate the capital of the Midlands.

I.M.S.

The I.M.S. no longer exists. Last month, along with the other great administrative Services of the Crown in India, the Indian Medical Service was disbanded. The Service may have come to an end, but its traditions will long survive, and it is a sign of the troublous times in which we live that the passing of this great Service should have been allowed to occur with so little notice being taken of it. Its place in the annals both of medicine and of India will always be an honoured one, and it is to be hoped that in time some memorial will be forthcoming to commemorate this important occasion in the history of British medicine.

WILLIAM A. R. THOMSON

London, September, 1947.

## CANADIAN MEDICAL WAR SERVICES

### MEDICAL OFFICERS STRUCK OFF STRENGTH OF THE R.C.A.M.C.—ACTIVE FORCE JUNE AND JULY, 1947

(Previous sections in January, March, April, May, June, July, September, October, November and December, 1945 and January, March, May, June, July, August, September, October, November and December, 1946 and January, February, March, May, June and August, 1947.)

#### SECTION XCIII

Name	Address	Date struck off strength
Boright, R. R.,	1040 Main St., Waterloo, Que.	31-5-47
Corbin, M. F.,	232 Heath St. W., Toronto	24-4-47
Cownie, D. H.,	4872 Cote des Neiges Rd., Montreal	24-4-47
Horner, E. B.,	Charteris, Que.	23-5-47
Hubar, M.,	283 Gottingen St., Halifax	17-6-47
Hunter, J. E.,	Ottawa	18-2-47
Johnston, G. M.,	34 Alwington, Kingston, Ont.	31-3-47
Knox, R. E.,	734 West 13th Ave., Vancouver	25-4-47
Luton, R. M.,	79 Stanley St., St. Thomas, Ont.	14-4-47
Ostiguy, L.,	282 Sherbrooke St. E., Montreal	15-4-47
Patterson, L. J.,	826 Walker St., Prescott, Ont.	5-3-47
Pion, P. P.,	3492 Vendome St., Montreal	8-5-47
Roy, J.,	Pike River, Missisquoi Co., Que.	10-6-47
Rutenberg, L. I.,	5335 Park Ave., Montreal	31-3-47
Shulman, A. J.,	123 Lauder Ave., Toronto	2-6-47
Stephenson, R. G.,	St. Walburg, Sask.	23-12-46
Van Kleeck, W. M. (Wilson),	Armstrong, B.C.	22-11-46

## ABSTRACTS FROM CURRENT LITERATURE

### Medicine

**Cerebral Angiomata in an Icelandic Family.** Kidd, H. A. and Cummins, J. N.: *The Lancet*, 1: 747, 1947.

These authors report a very interesting family from Iceland, two members of whom died in England, and on whom they secured autopsies. In both, there were extreme amounts of cerebral hæmorrhage, so profuse in one case that it was impossible to find the angiomatous vessels, which were demonstrated, however, in the other patient. They secured the rest of the family history from a doctor in Iceland. The family starts with four sisters, all of whom died in old age from apoplexy. One of them had a stroke at 20, but recovered, to die at 59 of another stroke. One of these sisters married twice. By her first husband she had 6 children, of whom two, a son and daughter died at 36 and 30 of cerebral vascular accidents. The son had two daughters, one of whom had 2 attacks at the ages of 31 and 33, and died of the second. The daughter had 5 children, of whom 3, 2 sons and a daughter died of cerebral hæmorrhage at the ages of 22, 23, and 23 respectively.

By the second marriage of the woman in the first generation, she had a son who died at 42 of stroke. He in turn had 5 children, three of whom died at the ages of 25, 27, and 29 of stroke. Stroke is a common mode of exit among the old, but it is most unusual to have it affecting and claiming the lives of the young. Ten of 19 persons died of this cause, mostly in their 20's, and the autopsy on two of them indicated that it was the rupture of angiomatous vessels that caused death.

MADGE THURLOW MACKLIN

**Congenital Essential Thrombopenic Purpura. Report of the Disease in Fraternal Twins.** Goldstein, L. S.: *Am. J. Dis. Children*, 73: 575, 1947.

The criteria for this disease have been set forth as (1) purpura with petechiae; (2) increased bleeding time; (3) increased time for clot retraction; (4) decreased platelets; (5) no change in coagulation time; (6) no change in prothrombin time; (7) normal or increased megakaryocytes; (8) normal vitamin C content of blood; (9) positive tourniquet test; (10) normal or large spleen; (11) no adenopathy; (12) leucocytosis; (13) no lymphocytosis; (14) no leukopenia. These twins, which were fraternal, a boy and girl, both had this condition. The mother although not having purpura, did have a slightly lowered platelet count, (182,000 in place of the normal 200,000 to 400,000). It has been said that no child exhibits a purpura unless the mother also shows it, but this is apparently not so. It probably is based upon a genetic factor.

MADGE THURLOW MACKLIN

**Diagnosis of Generalized Amyloidosis by the Congo Red Test: Definitive Diagnostic Criteria.** Selikoff, I. J.: *Am. J. M. Sc.*, 213: 719, 1947.

Sixty-one patients suffering from pulmonary tuberculosis were studied in an attempt to evaluate the efficacy in the diagnosis of amyloidosis of the Congo Red test. The cases were otherwise investigated in the usual routine manner. Tests showing 0 to 89% absorption in 1 hour were considered on a basis of the further clinical and in some instances the biopsy or postmortem findings as inconsequential. Those with 90 to 99% proved "suggestive" of amyloidosis. Tests showing 100% absorption were shown to be correctly "positive" in most cases.

Repeating the Congo Red test is advocated. In the author's experience no case showing complete or nearly complete absorption on recheck has proved to be other than amyloidosis. Details are given of cases showing 100% absorption on the first determination in which sub-

sequent study proved this to have been a "false positive" finding and quote similar experiences from the literature. In the case records given the recheck tests have been done as early as a month apart without recorded ill effect.

G. A. COPPING

**Subacute Combined Degeneration of the Spinal Cord Occurring in Identical Twins.** Schwarz, G. A. and Todd, J. C.: *Am. J. M. Sc.*, 214: 94, 1947.

Two identical twin brothers aged 57, showed degenerative changes in the spinal cord associated with gastric achlorhydria, and pernicious anæmia changes. They were diagnosed as identical on the basis of palm prints, such identity of appearance that the authors had difficulty in distinguishing between them, identity in all blood types, being A, MN, Rh, Rh' Hr', and had lipomata in identical situations over the body. Their father who lived to be 83 also had lipomata; the mother had died at 40. They had had one sister die at 3 months of congenital heart disease, and another sister die at 54 of abdominal tumour.

MADGE THURLOW MACKLIN

**The Oral Administration of Penicillin in Dogs.** Stebins, R. B., Macek, T. J. and Daughenbaugh, P. J.: *Am. J. M. Sc.*, 213: 671, 1947.

By *in vitro* experiments, using artificial gastric juice, it was shown that the speed of inactivation of penicillin by such a medium can be reduced by the addition of various buffer substances such as antacids and proteins. It was found that in dogs the simultaneous administration of oral penicillin with disodium phosphate, sodium acetate, trisodium citrate, calcium carbonate, etc., or with skimmed milk powder, egg albumen powder, whey powder, caused a marked increase in the total urinary penicillin excretion per 24 hours over that resulting from the administration of the same dosage in water alone.

Preliminary courses of the protective substances given prior to its administration were without effect in increasing penicillin absorption. Unfortunately, the number of animals used in each of the experimental groups is not given. It would appear from the figures, however, that the penicillin in water showed a rapid, though small, absorption leading to a high blood level which quickly fell away, while the various buffer substances allowed a perhaps less rapid absorption which was more maintained to a total greater absorption and to the maintenance of, in many instances, therapeutically active blood levels.

G. A. COPPING

**Sulfathiazole in the Abnormal Human Biliary Tract.** Zaslow, J. and Counseller, V. S.: *Am. J. M. Sc.*, 213: 68, 1947.

Following the lead given by other investigators in testing the penicillin and streptomycin levels reached within the lumen of the gallbladder and in the biliary ducts following systemic administration, these authors investigated the possibilities of sulfathiazole in this regard. They determined the gallbladder contents of 25 cases upon whom cholecystectomy had been performed, the patients having been given 3 gm. of sulfathiazole prior to operation.

In the cases with obstruction to the cystic duct no sulfathiazole was recovered from the gall bladder; where the duct was patent the drug was found to be present in the gall bladder contents. Studies upon the sulfathiazole content of the bile from T-tube drainage of patients who had been subjected to choledochostomy showed that the drug was excreted in the bile of those patients who were free of liver disease with impaired excretory function. Temporary delay in its appearance was in two cases ascribed to the hepatotoxic effect of anæsthesia and operation.

G. A. COPPING

**Cancer of the Rectum.** Ottenheimer, E. J.: *New England J. Med.*, 237: 1, 1947.

In 1935 Connecticut, through the co-operation of all bodies concerned, instituted a careful reporting and follow-up study on all cases of cancer. This has pro-



vided an excellent medium for the accurate appraisal of cancer statistics. The present review is concerned with the 1,610 cases of cancer of the rectum recorded over an eleven year period. Of these 1,610 cases, 1,188 were proven microscopically, the remainder being clinically diagnosed. The average age at time of diagnosis was 61.3 years. The average delay between onset of symptoms and diagnosis was between 6 and 11 months. Careful digital examination suffices to make the diagnosis in the majority of cases while proctoscopic examination and biopsy are only necessary in a small number. X-ray examination has a wide margin of error as a diagnostic method.

The usual presenting symptoms are rectal bleeding, loss of weight and change in bowel habit. Local pain and tenesmus are also frequent. Only 11% of the cases gave hemorrhoids as the first symptom and many of these were treated surgically before cancer was suspected.

Radical resections were performed in 38.5% of all cases. Local excision was done in 49 cases (usually malignant polyps). Only 2.7% were treated by radiation alone although this method was combined with surgery in a number of patients. The operative mortality in 275 colostomies was 28% but study of the records suggested that radical resections could have been performed in 25% of the colostomy cases had they been in the care of more skillful hands.

Of the 621 resections, 74.6% were done in one stage and it was worthy of note that the single stage operation became increasingly frequent and formed over 90% of all resections in the final three years of the study.

The increase in the resections over the years was accompanied by a lowering of operative mortality. From 1935 to 1940 the operative mortality was 24.9% in 237 cases but fell to 18.4% of 384 cases from 1941 to 1945. The mortality for two-stage resections increased slightly in the latter period obviously because it was reserved for the more serious type of case.

For the six-year period 1935 to 1940, five-year cures were obtained in only 7.9%. Improvement in operability and mortality rates as the years passed were attributed to the use of antibiotics, better management of shock and phlebitis and the more widespread employment of trained physician-anæsthetists. It is suggested that further improvement would result if these cases could be concentrated in a few centres. Earlier diagnosis of cancer of the rectum is essential and biopsy should be performed in all cases if an accurate appraisal is to be made.

NORMAN S. SKINNER

#### **Infectious Hepatitis with Subacute Atrophy of the Liver.** Jersild, M.: *New England J. Med.*, 237: 8, 1947.

An epidemic of infectious hepatitis occurred in Copenhagen in 1944-45. In a single hospital department 123 cases were seen during this period. Only one male patient was noted and in the women practically all were past the menopause (79% being over 50 years of age). The course of the disease was protracted with a high mortality rate of 61%. The cause of the epidemic was suspected to have been a special malignant virus and since women after the menopause were particularly affected the question is raised whether oestrogens exert some form of liver-protecting influence against this particular infection.

NORMAN S. SKINNER

#### **Pregnancy Following Lumbodorsal Splanchnicectomy for Essential and Malignant Hypertension and Hypertension Associated with Chronic Pyelonephritis.** Newell, J. L. and Smithwick, R. H.: *New England J. Med.*, 236: 851, 1947.

Pregnancy occurring in the face of pre-existing hypertension carries a notoriously poor prognosis for both mother and infant and the excellent results here reported of the benefits which splanchnicectomy confer on such cases is of interest. Of the 14 cases in the series the blood pressures prior to splanchnicectomy averaged 196 systolic and 130 diastolic. The time elapsing between splanchnicectomy and pregnancy averaged 31 months,

with the exception of one case in which the operation was performed during the first trimester of pregnancy. The average age at time of delivery was 31 years and the average parity was 2.3. In 9 cases the blood pressure during pregnancy remained within normal limits and there was no albuminuria. The other 5 patients showed no significant elevation of blood pressure until the third trimester, when 2 developed marked elevation (above 180 systolic). Marked albuminuria in one of these necessitated interruption of pregnancy at the thirty-fourth week. Normal deliveries occurred in 11 cases and Cæsarean sections were done in 3, the indications for section being a previous hysterotomy in two cases and fulminating pre-eclampsia in another. Thirteen babies are living and well, 2 having been premature, and there was one still-birth as the result of premature placental separation. The puerperium was uncomplicated in all cases except one where a post-partum psychosis developed.

NORMAN S. SKINNER

#### **Disturbances of Metabolism Associated with Head Injuries.** Pickles, W.: *New England J. Med.*, 236: 858, 1947.

While not a common sequela, head injury can result in metabolic upset. Seven such cases occurred among 2,500 patients with injuries to the head. It is probable that minor metabolic disorders may frequently pass unsuspected in such patients.

Of the 7 cases of metabolic upset, 2 involved sugar metabolism, 4 water and 1 fat metabolism. One case of transient glycosuria later developed diabetes insipidus and a case of mild diabetes was temporarily made insulin-resistant by the effect of his head injury. Four cases of diabetes insipidus showed persistence beyond a few weeks in only a single case. A single patient with lipæmia and increased blood cholesterol became apparently normal after about twelve months of observation. No evident case of disturbed protein metabolism was found.

NORMAN S. SKINNER

#### **Airblock in the Newborn Infant.** Salmon, G. W., Forbes, G. B. and Davenport, H.: *J. Pædiat.*, 30: 260, 1947.

Six case reports are presented of infants in whom air in the pleural cavity or interstitial tissues of the lung and mediastinum was demonstrated as by roentgenography and at autopsy. In four of these infants a tracheal catheter was used in resuscitation. The authors think that pulmonary interstitial emphysema occurs in the newborn more often than is commonly believed, and urge pathologists to search for it specially. Interstitial pulmonary air can produce pneumothorax in newborn infants directly by rupturing the visceral pleura, or indirectly by first producing a mediastinal emphysema which in turn ruptures the mediastinal pleura. The pressure of a pneumothorax does not depend on its size. A pneumothorax may be under considerable tension, and yet the lung may be so splinted by interstitial air that it can collapse only moderately. In lateral roentgenograms a pneumothorax may simulate an apparent substernal pocket of air. On the other hand, considerable mediastinal emphysema may occur in the absence of this roentgenographic sign. The rôle of pulmonary interstitial emphysema, in producing air embolism, and also in contributing to cardiac malfunction, needs additional study.

C. C. MACKLIN

#### **Some Notes Concerning Angina Pectoris.** Levine, S. A.: *Bull New Eng. Med. Centre*, 9: 97, 1947.

The outstanding views which have been put forward to explain anginal pain are briefly noted. Mackenzie considered it due to myocardial weakness or exhaustion; Allbutt and Wenckebach thought it was due to aortitis; in Lambert's opinion the pain resulted from dilatation of the coronary artery proximal to the point of narrowing or spasm. Many have held that spasm of the coronary arteries is the responsible factor. The current view, first completely presented by Keefer and Resnick, is that anoxæmia of the heart



muscle is the cause of the anginal pain. There are many questions yet unanswered. What is the final noxious factor resulting from the anoxæmia? Where does the pain arise? What is the nature of the "trigger mechanism" when pain occurs in association with an emotional disturbance without any particular increase in the work of the heart? It is difficult to explain many anginal episodes purely on the relationship of the oxygen supply and the work of the heart.

With particular regard to the nervous "trigger" in the production of the anginal episodes, experience with the effect of carotid sinus stimulation is noted. In about 50 observed anginal attacks occurring during routine medical questioning, the carotid sinus of either side was stimulated. It was noted that when slowing of the heart took place there was complete cessation of the pain or a decrease in its severity. The effect might or might not persist. If no slowing resulted the pain was not influenced. Pain relief occurred in a few seconds. "In these observations, the relief of pain occurred so quickly that it seems more reasonable to explain the mechanism on a neurogenic basis and as the result of the release of spasm than as involving a chemical mechanism." Further investigation as to the relationship between carotid sinus stimulation and anginal attacks may throw light on the nature of the anginal pain.

A. L. JOHNSON

### Obstetrics and Gynæcology

**A Study of Two Transfusion Deaths Due to Rh Incompatibility.** Williams, B. F. P.: *Am. J. Obst. & Gyn.*, 54: 18, 1947.

Two deaths are reported attributed to transfusion with Rh incompatible blood. The details of treatment with autopsy findings are presented. Comparable cases from the literature have been reviewed and analyzed.

No conclusion is offered for the preferred method of therapy in transfusion reactions with uræmia.

ROSS MITCHELL

**On the Prophylaxis of Hæmolytic Disease of the Newborn.** Karcher, D. H.: *Am. J. Obst. & Gyn.*, 54: 1, 1947.

Three cases are presented in which an attempt was made to prevent hæmolytic disease of the newborn by means of intramuscular injections of ethylene disulfonate in distilled water into the mother *ante partum*.

In two of the cases normal infants were born while in the third case the infant suffered from hæmolytic disease but recovered after transfusion.

It is suggested that some non-specific tissue reaction may bring about a lowering of the serum antibody level, and thus prevent or modify the disease in the newborn.

A more suitable plan for aiding in the prognostication of hæmolytic disease of the newborn is outlined.

ROSS MITCHELL

**The Problem of the Repeat Cesarean Section—a Preliminary Study.** O'Connor, C. T.: *Am. J. Obst. & Gyn.*, 53: 914, 1947.

A review of the experience of individuals or of individual hospitals reveals that the mortality of repeat classical Cesarean sections has been in the past 3.2%. At the present time this risk probably can be reduced to about 1.5%. A review of similar experiences with the low operation reveals a mortality of slightly over 1%. In both procedures, second Cesareans bulk large, with a much smaller number of third Cesareans and practically none beyond this. It is highly probable that the danger would have been greater than 3.2% in classical, and 1.2% in low sections were a larger number of fourth and fifth Cesareans recorded.

The dangers of elective repeat section are both immediate and remote. The remote dangers of rupture of the uterine scar and intestinal adhesions are very marked after the classical section, and exist to a much less degree after the low section. A conservative type

of section with sterilization removes the danger of rupture of the scar and risk inherent in another future section, but does not diminish the immediate mortality due to the procedure, nor the immediate and remote dangers from adhesions. Evidence is presented that elective Cesarean hysterectomy is simple to perform, causes less blood loss, has a smoother convalescence and shows less morbidity than conservative repeat sections with or without tubal sterilization; and in addition, eliminates future dangers from a useless organ, the uterus.

The procedure should be given more consideration as an elective procedure at repeat sections, and should often be performed in the patient over 40 years of age; in the presence of poor scars; when the uterus does not contract perfectly; in the presence of marked adhesions; after the third or more classical section; and in patients who are subject to severe grades of heart disease, kidney disease or tuberculosis. Further experience may reveal it to be the procedure of choice routinely at or after the third section, even of the low type.

If the patient is a Roman Catholic and the surgeon believes that Cesarean hysterectomy is, for that particular patient, a safer procedure than any type of conservative section, he may in the opinion of some Catholic moral theologians perform the operation. The uterus need not be diseased to justify its removal.

ROSS MITCHELL

**Radiography as an Aid to Dose-Control in Radium Treatment of Cervix.** Hulbert, M. H. E.: *J. Obst. & Gyn. Brit. Emp.*, 54: 137, 1947.

Radiotherapy of cancer demands that the whole of the tumour-bearing tissue be irradiated with an adequate dose. When radium is being applied locally to the growth, notice should be taken of the fact that the intensity of radiation falls off very rapidly with increase in distance from each individual component of the radium assembly. The radium must, therefore, be arranged with precision if an adequate irradiation of the outlying parts of the tumour is to be achieved without causing damage to the tissues near the radium. The mechanical flexibility of the radium applicators used in the "Stockholm" type of treatment of cancer of the cervix allows easy adjustment of the configuration of any individual case. Charts were made and two points emerge on examining them. The very rapid decrease of intensity with an increase of the distance from the source, e.g.: intensity 1 cm. from the vaginal box, 150r/hr. Intensity 2 cm. from vaginal box, 40r/hr. For distances greater than about 2.5 cm. the isodoses closely follow circles which are centred on the centre of the box. This means that for such distances the dose is mainly governed by the distance from the centre of the box and is largely independent of any tilt or rotation of the box through its centre. In the Stockholm type of treatment by intermittent application it is reckoned that a total of 6,600 r given in three insertions represents an adequate dose. A dose smaller than 4,500 r must be regarded as insufficient.

P. J. KEARNS

### Surgery

**A Concept of Paralytic Ileus: A Clinical Study.** Devine, J.: *Brit. J. Surg.*, 34: 158, 1947.

A study of postoperative distension, constipation and vomiting was made over a period of six years using recordings made by the variations in pressure in the Miller-Abbott tube balloon, x-ray studies of the effects of various drugs on the normal bowel, and the histories and findings in 43 consecutive cases.

Paralytic ileus of unknown cause (idiopathic) may be due to (1) overaction of the sympathetic nerves as a result of stimulation as in retroperitoneal hæmatoma; (2) reflex inhibition of gut movement by an abdominal blow, peritoneal irritation, abscess, acute appendicitis or simply an abdominal incision. This type is relieved by spinal anaesthesia. Urinary retention and ileus are often associated in the same patient. Following a cathartic there is a period of intestinal

atony. Serum transfusion increases bowel motility when the serum protein is low. (3) Medical diseases, that is, any form of general infection or toxæmia, may cause paralytic ileus, e.g., anæmia, pneumonia, liver failure. (4) Surgical diseases may cause paralytic ileus. Intestinal obstruction is followed by ileus because long-continued distension leads to paralysis of the bowel. The presence of pus, urine, blood, bile, gastric, duodenal or intestinal contents in the peritoneal cavity causes bowel paralysis, first in one loop often.

Distension of the intestine by gas, which is mostly swallowed nitrogen, will cause venous obstruction which in turn interferes with the absorption of gas. The capillaries of the intestinal mucosa become more permeable when the bowel is distended, and large quantities of fluid high in protein may be lost into the lumen, further decreasing motility. Vomiting increases the loss of fluid, and also of sodium ion. Kinking of distended small bowel may result in mechanical obstruction at the apex of each loop. Distension also results in the weakening of longitudinal and circular muscle.

Treatment of paralytic ileus by stimulation of the bowel is now going into disrepute. If cathartics work, the patient has not got paralytic ileus. Ileostomy drains only the segments in which it is placed. Continuous gastric or intestinal suction by the Miller-Abbott tube and intravenous fluids and the oxygen tent are most popular recently. Pituitary extracts are effective in increasing colon motility but doubtfully affect small intestine. Parasympathetic stimulants such as prostigmine and acetylcholine may be of use in prophylaxis against ileus. Vitamin B complex is useful in chronic constipation. Bile salts or bile increase the propulsion through isolated loops of dog's intestine. Enemas are the most effective stimulative treatment to a small bowel capable of response. Heat has no effect in increasing intestinal motility. Morphine has a useful place in treatment as it increases small mixing peristaltic waves and increases muscle tone. Atropine and hyoscine decrease small intestine tone. Barbiturates and aspirin have been found to decrease intestinal movement.

There are three stages of ileus: (1) stage of no movements; (2) stage of disordered and unco-ordinated movement; (3) stage when movement is being co-ordinated once more. The second stage is shown by the gas pains seen post-operatively.

Prophylaxis is suggested: (1) no preoperative cathartics; (2) gentle manipulation during operation and never leave packing in the peritoneal cavity; (3) never force fluids within twelve hours after operation; (4) avoid atropine and barbiturates, use morphine post-operatively; (5) avoid enemas, pituitrin, eserine during the first and second stages of ileus postoperatively (normally four days in duration).

Fully developed cases of paralytic ileus should be treated with morphine four hourly and an indwelling duodenal tube. The Miller-Abbott tube "travelling ileostomy" is life-saving when the abdomen is distended and silent, and if it cannot be manipulated past the pylorus, it should be passed into a jejunostomy. Replacement therapy should include a litre of serum and 2,900 c.c. of fluids: 2 litres of 5% glucose in saline plus a litre of 5% glucose intravenously. When the tube is in the intestine the patient should be fed a high carbohydrate, high-protein diet. BURNS PLEWES

#### Peritoneal Irrigation for Uræmia Following Incompatible Flood Transfusion. Muirhead, E. E. et al.: *Arch. Surg.*, 54: 374, 1947.

In 1946, Frank, Seligman and Fine reported a favourable results after treating by peritoneal irrigation, a patient with uræmia resulting from acute renal damage following sulfathiazole therapy.

Recently, Muirhead and his co-workers utilized this method of peritoneal irrigation on a patient with uræmia resulting from an incompatible blood transfusion, with a favourable result. They record a case history of this patient. The prognosis seemed poor until Frank, Selig-

man and Fine's method was instituted. The amount of urea cleared from the body by this procedure was comparable to that reported by these observers. The urea clearance was taken as a measure of the clearance of other substances. Overhydration constituted one of the main complications, as the kidneys were not able to discard water. Recovery was associated with the loss of water and salt from the body, while dextrose in distilled water was used for peritoneal irrigation.

G. E. LEARMONTH

#### Bilateral Lobectomy for Bilateral Bronchiectasis.

Bisgard, J. D. and Swenson, A. Jr.: *Arch. Surg.*, 54: 483, 1947.

The mortality rate for unilobar bronchiectasis has declined to the present regular level (less than 1% in a recently reported series), so that the indications for the operation have been extended to include two types of cases which in the past were rejected; namely: (1) Cases of minimal disease with symptoms not troublesome enough to warrant any considerable risk of operation and (2) cases of diffuse disease, with involvement of both lungs or of both the upper and lower lobe of one lung. This article is concerned with the second type only, where there is multilobar disease with a more urgent need of surgical intervention, because, in general the more widespread the disease, the more severe are the symptoms.

The mortality of lobectomy for bilateral disease is higher than that for unilateral disease due in great measure to the greater quantity and spillage of pus also of secretions into the bronchial tree during operation. In cases of unilateral involvement all disease is eradicated at the time of the original operation but in cases of bilateral bronchiectasis a portion of the diseased and pus containing bronchi remain to complicate convalescence. In 37 instances of bilateral lobectomy collected from the literature, there was a mortality of 13.5%.

The authors report the records of four patients with bilateral bronchiectasis cured by bilateral lobectomy. In all, the lower lobes of both lungs were removed and in one patient the middle lobe of the right lung was also excised.

G. E. LEARMONTH

#### End-Result Study of the Intervertebral Disc. Lenhard,

R. E.: *J. Bone & Joint Surg.*, 29: 425, 1947.

The author has carried out a survey of a series of 843 patients by means of a questionnaire as to symptoms.

These patients had all been operated on for low back pain by the removal of the intervertebral disc. While the answers were simply "yes" or "no", it is of interest to note that few of the patients were entirely relieved of all symptoms so that they could be classified as having excellent results, able to perform their normal activities without complaint. The results were therefore summarized as good, improved, or not improved.

The results obtained were that 67½% of the patients returning for examination showed good results, while of those not examined good results were obtained in 59.5%, giving an average of 63.5% with good results; 19.9% improved; and 16.5% not improved. Several of these patients had had repeated operation for recurrences of pain. The residual complaints of the patients were numbness of the leg, cramping of the leg or foot, weakness of the back with excessive activity, or stiffness after being at rest.

GUY H. FISK

#### The Pathology of Ununited Fractures of the Neck of the Femur. Sherman, M. S. and Phemister, D. B.: *J. Bone & Joint Surg.*, 29: 19, 1947.

The authors discuss the causes of non-union in intracapsular fractures of the neck of the femur. This discussion is based on a very complete examination of some 8 cases treated by them.

The incidence of non-union is disproportionately high in intracapsular fractures of the neck of the femur, except in those which are either impacted or treated by accurate reduction and internal fixation.



Factors entering into this high incidence are the frequent occurrence of death of the head fragment from disruption of the blood vessels of the neck, displacement of fragment ends, poor immobilization, and failure of peripheral callus formation due to absence of a cambium layer on the neck.

If the head fragment survives, it undergoes atrophy of disuse of the same degree as that of the distal fragment, and the two fragments are of equal density on the roentgenogram. Treatment to produce union is usually successful and extensive degenerative changes in the joint do not occur. If the blood supply to the proximal fragment is severed, so that the head dies, disuse atrophy cannot occur, and the head eventually appears on the roentgenogram to be more dense than the surrounding atrophic, living bone. As slow invasion of the head by vascular fibrous tissue occurs, with absorption of the necrotic bone and replacement by cancellous new bone, the roentgenogram shows areas of reduced density.

If union has occurred, either primarily or as the result of surgical intervention in the presence of a dead head, and if weight-bearing is begun before replacement is complete, the head will probably collapse, and degenerative changes will be severe on both sides of joint. If the head is adequately protected, it may be transformed without any collapse; the degenerative changes in the joint are minimal; and a good functional result is obtained.

GUY H. FISK

### Dermatology

**Disseminated Lupus Erythematosus and Diffuse Scleroderma.** Baehr, G. and Pollack, A. D.: *J. Am. M. Ass.*, 134: 1169, 1947.

In disseminated lupus erythematosus, diffuse scleroderma, and less conspicuously in allergy, serum sickness, periarteritis nodosa and rheumatic fever fibrinous degeneration of collagen in the connective tissues, and various resulting vascular and visceral lesions, appear to be morphologic phenomena common to all. From this it has been implied that the diseases are related or have a somewhat similar cause. The authors reconsider the clinical and pathological manifestations of the first two diseases, and re-examine the evidence regarding their possible relationship with the other so-called "collagen diseases" and more specifically with allergy. The fibrinoid degeneration of collagen in the vascular walls, the subendocardial and epicardial connective tissue and the glomeruli are identical in disseminated lupus erythematosus and diffuse scleroderma. But the clinical pictures presented by the two diseases are quite dissimilar. In the skin of scleroderma, while areas of fibrinoid degeneration may be found microscopically the predominant change throughout its course is diffuse sclerosis. The characteristic sex predominance of lupus erythematosus is also lacking. Fibrinoid degeneration of collagen fibrils has been described in the Arthus phenomenon, after sensitization to bacterial or homologous serum antigens, and in serum sickness, and by some it has been assumed that all lesions showing this change are essentially of allergic character. However typical fibrinoid degeneration is commonly seen in the walls of the arteries in malignant hypertension, and can be produced experimentally in animals in whom arterial hypertension is induced by the Goldblatt experiment, where there is no question of allergy. There is therefore insufficient ground for assuming that disseminated lupus erythematosus and diffuse scleroderma must be the result of hyperergic states induced by an unknown agent. Clinical evidence, such as the absence of eosinophilia, urticaria, asthma and other allergic phenomena is also lacking in lupus erythematosus. This is a contrast to periarteritis nodosa which in many instances is manifestly due to allergy. The collagen degeneration in this disease however is limited to the vessel walls, and in the accompanying inflammatory reaction of adventitia and media eosinophils are conspicuous. At times fever and arthritis may be the only clinical manifestations of disseminated lupus erythematosus making its differentia-

tion from rheumatic fever difficult, but the leukopenia, cutaneous, oral and retinal lesions, clinical evidence of renal vascular injury and almost exclusive female predominance are not seen in rheumatic fever. In the latter the foci of collagen degeneration are limited chiefly to the perivascular spaces of the myocardium, in the subendothelial layers of the valves and only occasionally in vascular walls.

The authors' conclusion is therefore that fibrinoid degeneration of collagen is not a sufficiently specific pathologic process to serve as a reliable common denominator for the classification of a disease, nor warrants the grouping of all such diseases into a common category of allergic diseases; also that in spite of their common similar morphologic expression in the fibrinoid degeneration of collagen and identical lesions of blood vessels, glomeruli, endocardium and serous and synovial membranes, their clinical dissimilarity does not support the view that they are related to each other, or to the other diseases in which similar collagen changes may occur as part of the pathologic process.

D. E. H. CLEVELAND

**Chronic Erysipelas (Swine Erysipelas) in a Man. The Effect of Treatment with Penicillin.** Stiles, G. W.: *J. Am. M. Ass.*, 134: 953, 1947.

Swine erysipelas, of which the infective agent is *Erysipelothrix rhusiopathiae*, and which is known in man as erysipeloid, is usually contracted by contact with diseased animals or their products, as encountered on the farm, in the abattoir, the laboratory and the fishing and fish-packing industries and the button factory. Diagnosis is established by positive reactions with swine erysipelas antigen in titres of 1:50 and upward. In the case presented the patient, a healthy farmer of 27, had been handling swine from a herd in members of which swine erysipelas had been demonstrated. In the course of his work an initial infection was acquired on the thumb. A small vesico-papule was followed by a diffuse deep livid erythema spreading over the hand, later to the other hand and in a few months to the feet. Sloughing occurred, particularly on the palms, accompanied by an offensive odour and intense itching. Suppuration did not occur. There was temperature rising occasionally to 101.6° F., occasional chills, mental depression, anorexia, weakness, much loss of weight and rheumatoid pains. Some improvement occurred following radiotherapy and topical medication, after 9 months, but crops of small vesicles continued to appear on feet and hands. Four years later complete relapse occurred, cultures for bacterial and mycotic organisms from the skin were negative, but after the use of sulfathiazole ointment improvement, back to the stage of vesicular dermatitis took place. Finally, chance led to his blood being tested for possible erysipeloid infection, and positive reactions in titres of 1:25, 1:50, 1:100, 1:200 and 1:400 were disclosed. Repeated efforts failed to demonstrate *E. rhusiopathiae* in the contents of the vesicles. Injection of 25,000 units of penicillin every 3 hours until 600,000 units had been given was followed by cure. The condition which had been present for nearly 9 years prior to treatment did not recur during 2 years of subsequent observation. One year after treatment the patient's blood was negative to the *E. rhusiopathiae* antigen in concentrations of 1:25 and upward.

D. E. H. CLEVELAND

**Prophylaxis of Cancer.** Adair, F. E.: *Bull. N.Y. Acad. Med.*, 23: 383, 1947.

The problem is fundamentally linked to the cause of cancer. There are two basic attributes in the production of cancer: the *intrinsic* factor—elements inherited within the cell itself; the *extrinsic* factor—the environment of the cell which influences cell life and growth. Among intrinsic factors belong Cohnheim's theory of the inclusion rest. Von Recklinghausen's disease with its frequent concomitant sarcoma, hairy pigmented nevi and even melanoma should be considered the result of



intrinsic factors. The intrinsic factor may be produced by external agents, such as radiating the germ plasm modifying certain chromosomes and genes. Chronic irritation, virus-like bodies, actinic and radioactive rays, carcinogenic chemicals, thermal, mechanical and parasitic trauma are environmental or extrinsic factors. In the case of the effect of sunshine on the skin the author is of the opinion that this is not nearly so important in the young as in those past middle age and on aging skin. As skin cancer is easiest of all types to cure all precancerous lesion should be removed from the skin. Low voltage x-rays applied to the skin frequently results in cancer, often as late as 20 years afterwards. Melanoma should be surgically widely removed and not by *in situ* destruction by electro-desiccation. Every large skin burn which does not heal well should be grafted. This will prevent cancer in almost 100% of burn scars. This also should be done to radiated areas of lupus if they appear suspicious. A new group of skin cancers is being observed on the hands of workers in gasoline service stations, which has resulted from neglect to scrub tar, oil and gasoline from the dorsal surface of the hands. Of all types of cancer the intra-oral group is the most easily prevented, by smoothing down sharp, broken or unaligned teeth, sharp or rough spots on the dentures, reducing oral infection and avoiding burning from excessive smoking. The treatment of syphilis, a notorious basis for intra-oral cancer, should be considered in this respect a prophylactic measure.

D. E. H. CLEVELAND

**The Effect of Restricted Intake of Carotene and Vitamin A on Psoriasis Vulgaris. A Preliminary Report.** Hoffman, R., Lorenzen, E. J. and Garfinkel, A. S.: *New Eng. J. Med.*, 236: 933, 1947.

In psoriatic skin increased demands on the protective and reparative processes of the epidermis result in failure of the mechanism of keratinization and resulting parakeratosis. In the view of Grütz and Bürger psoriasis is a "lipoidosis" and in accordance with this they believed that improvement resulted from a low fat diet, by lowering the fat content of the skin. Their views have not met with general acceptance however, especially on theoretic grounds. It is suggested by the authors that any improvement resulting might be due to simultaneous reduction in the intake of vitamin A. Eleven cases with extensive psoriasis of the chronic type which had shown no tendency to spontaneous remission were put on a diet permitting maximal daily intake of 150 to 300 international units of vitamin A. No foods containing an average of more than 50 units per serving of vitamin A were allowed, while foods free of this vitamin were freely permitted. Supplements of vitamin B complex, ascorbic acid and iron were added to the diet in most cases. Patients were specifically instructed to take sufficient vitamin A-free fats to compensate for omission of fats containing this vitamin. Local treatment was restricted to soft paraffin. In 9 of the 11 cases the eruption markedly decreased or cleared entirely in 8 to 10 weeks. In 6 patients relapses occurred within 3 to 8 weeks after resuming normal diet, and in 1 patient 6 weeks after supplementing the restricted diet with carotene. Withdrawal of carotene again was followed by marked improvement in 2 weeks. The dietary restriction is not considered to be a practical therapeutic regimen, but establishes a base for further investigation which is being continued. It appears to show that the results following the low fat diet of Grütz and Bürger are not due to reduction of cellular fat content of the epidermis, but it cannot be stated definitely as yet that stimulation of keratinization due to vitamin A restriction is the basis of the observed improvement.

D. E. H. CLEVELAND

**The Management of Urticaria Due to Penicillin.** Pillsbury, D. M., Steiger, H. P. and Gibson, T. E.: *J. Am. M. Ass.*, 133: 1255, 1947.

Urticaria is the most frequently encountered reaction to sodium penicillin administered parenterally.

Reactions occur more frequently in patients who have had repeated courses of the drug; some patients who have had urticarial reaction may tolerate penicillin, others may not; skin tests with penicillin are unreliable as means of predicting reactions; anti-histamine compounds, especially benadryl are useful in controlling penicillin urticaria. The writers have found that it is sometimes possible to continue penicillin therapy in a reacting patient by the simultaneous administration of an antihistamine compound. Again such compounds may fail to control the urticarial reaction, which may be accompanied by severe gastrointestinal symptoms which may be re-precipitated by administration of small doses of penicillin. Nevertheless cases are encountered in which resumption of full doses of penicillin after the urticarial reaction has been controlled is not accompanied by urticaria. Severe urticarial reaction to penicillin, accompanied by asthma, responding only moderately to pyribenzamine or benadryl, was observed, followed by unexplained ecchymoses and bleeding from uterine and other mucosal surfaces. In urticaria due to penicillin the authors recommend immediate interruption of the penicillin unless there is an immediate critical need for the drug, and oral administration of benadryl or pyribenzamine in doses to adult patients of 50 to 100 mgm. thrice daily. Twelve hours is sufficient time to estimate its efficacy and increase in frequency of dosage may be necessary. If the allergic symptoms subside penicillin may gradually be resumed, starting with a test dose of 1,000 units of penicillin of another manufacturer's product, increasing to 10,000 to 20,000 in 6 hours, and if no reaction occurs in 4 hours full dosage may be resumed. The dosage of the anti-histamine compound is gradually reduced, but resumed in the dosage formerly found effective if urticaria reappears. The penicillin during the trial administration should be given in a form rapidly excreted.

D. E. H. CLEVELAND

## Pathology

**The Carcinogenic Action of Smegma.** Plaut, A. and Kohn-Speyer, A. C.: *Science*, 105: 391, 1947.

Carcinoma of the penis is rare in persons circumcised in childhood or in early puberty, but no such protection is conferred by circumcision in adult life. On the basis of this knowledge, and the recognition of phimosis as a predisposing factor the carcinogenic action of smegma was investigated. Human smegma in sufficient amounts being unobtainable, horse smegma was selected as a substitute on account of the frequency of penile cancer in the horse. The non-saponifiable fraction as well as whole smegma was used, with cerumen, which resembles smegma in being a skin product retained on or near the body surface, as a control, because carcinoma of the auditory meatus is rare in men and animals. Mice were used as subjects and the whole smegma injected into a buried skin tunnel in the midline of the mid-dorsal region, having walls consisting of skin and panniculus carnosus. Whole smegma was also injected into the skin of other mice, and in others the non-saponifiable fraction was painted into the tunnel or the skin surface. Four hundred mice were treated with smegma, in 88 of which the non-saponifiable fraction was used. Microscopic sections of skin and inner organs were available in 212 of the 400 smegma-treated mice and 80 of the 150 controls. Lung adenomas occurred 15 times in the treated mice and twice in the controls. For lymphoid tumours and leukæmia the figures were 15 and 5. Mammary carcinoma occurred 21 times in 105 treated females and 3 times in 40 female controls. There were 6 other spontaneous tumours of various kinds in treated mice and 2 in controls. No tumour was found at the site of treatment in any control mouse. Eight tumours occurred at the site of treatment in smegma-treated mice, and of these 4 were frankly malignant, one having intrathoracic metastases. There was no indication of the possible nature of the carcinogenic

factor in smegma. The chemical composition and precise origin of smegma is as yet not a matter of common agreement.  
D. E. H. CLEVELAND

**Mechanism of the Invasiveness of Cancer.** Coman, D. R.: *Science*, 105: 347, 1947.

It has been thought that chemical and physical differences must exist between benign and malignant neoplastic cells which permit the former to remain localized and the latter to invade adjacent normal tissues. It has been shown that attached pairs of cancer cells can be separated from each other by micro-manipulation through the application of much less force than is required to separate normal or benign tumour cells. Such relatively feebly coherent cells should therefore be able to wander into adjacent parts by ameboid movement. It has also been shown that the absence of calcium from the medium in which normal squamous epithelial cells are immersed reduces their adhesiveness, and methylcholanthrene which directly reduces the calcium content of epithelial cells also reduces their adhesiveness. It is therefore concluded that the decreased adhesiveness of cancer cells of the squamous epithelial variety is dependent upon their low calcium content. In the study of epithelial cells from human carcinomas in tissue culture it was found that individual cells frequently became detached from sheets or clusters of epithelium and were actively ameboid, progressed some distance away from the parent mass and built up new colonies. This occurs in cells from both sarcomas and carcinomas. The detached ameboid malignant cell is thus physically adapted to invasion of surrounding tissues, and the softening of intercellular cement substance by spreading factors, such as hyaluronidase, in malignant tumours would further facilitate the invasive action of the latter. It has not yet been demonstrated that the cancer cell itself contains hyaluronidase, or what the origin of the spreading factor within the tumour is. Significant amounts however have been revealed in several instances. It has not been demonstrated that spreading factors of this type are essential to invasiveness, but it is quite possible that this third factor, added to the two factors of decreased adhesiveness of cancer cells and their powers of ameboid movements, when it does operate, augments the facility with which invasion occurs.  
D. E. H. CLEVELAND

### Radiology

**Carcinoma of the Skin: Influence of Dosage on the Success of Treatment.** Hale, C. H. and Holmes, G. W.: *Radiology*, 48: 563, 1947.

Tabulation of the results of the single massive dose method of irradiation in carcinoma of the skin, over the range of the various doses used, showed that 1,200 to 1,800r gave only an 81% chance of destroying the lesion. The administration of 1,900 to 2,200r did not offer better than an 85% chance, while the delivery of 2,400r might raise the expectancy to 91%. A constructed curve showed that a lesion was as likely to be destroyed with a 2,500 to 2,800r range as with the delivery of 4,000r. In the group of cases studied, therefore, approximately 2,700r may be considered the optimum dose, since it produced as satisfactory results as higher dosages and at the same time might be expected to leave the irradiated area in better condition.

Comparison of results obtained by multiple treatments within the period of one week and by the massive single-dose method indicates that 3,200 to 3,600r must be delivered by the former method to produce the same results as were obtained by 1,900 to 2,200r by the latter. Approximately 4,500r delivered in multiple treatments within one week produced essentially the same results as 2,700r given at one time. This dosage, 4,500r is suggested, therefore, as the optimum dose to be delivered to a carcinoma of the skin when the fractionated method (within one week) is to be used.

Twenty-six late radiation ulcerations were observed following the treatment of lesions which were not extensive in size and which did not receive more than a single treatment, or a single course of treatments; 92% developed following the use of heavily filtered radiation (half value layer 0.6 mm. Cu), while only 61% of the total lesions were so treated. The roentgen dosage responsible for these ulcers would not be considered excessive by most standards. The fact that late radiation ulceration does develop following the treatment of a small lesion with a relatively small amount of radiation makes questionable the routine treatment of all skin cancers with an excessive dose of radiation in the false hope of obtaining perfect results. The chance of destroying the lesion with a much smaller amount is essentially as good as with the tremendous dosage, and the danger of subsequent complication to the patient is much less. If necessary, the few lesions that may recur because of inadequate dosage may be successfully treated later by surgical removal.  
R. C. BURR

### Industrial Medicine

**Byssinosis in the Cotton Trade.** Gill, C. I. C.: *Brit. J. Indust. Med.*, 4: 48, 1947.

In this article the author presents information regarding byssinosis, a respiratory disease, affecting workers inhaling dust in cotton mills. No specific appearances diagnostic of byssinosis were detected in x-ray films of 100 patients. It would appear that the x-ray film cannot therefore be used as a pointer to diagnosis; it rests on a history of exposure for many years, on the patient's symptoms and on clinical examination. The operators in charge of the carding engines—the strippers and grinders—are the principal sufferers. There is very strong evidence that the dust liberated by the carding process in the immediate vicinity of the carding engine contains the injurious element or elements causing byssinosis.

In describing the symptomatology, and the physical and radiographic appearances, the author differentiates between the early and late stages of the disease. The early stage, which manifests little or no constitutional disturbance, is the condition commonly called mill fever or Monday morning fever and is known to many card-room operators. After a short time many operators seem to become immune. This superficial irritation of the bronchial mucous membranes by the cotton dust rarely progresses further except in strippers and grinders. Among these latter operators however, will occur serious respiratory damage. The symptoms gradually reappear 10 or 20 years after the earlier attacks, and increase in severity and duration, leading to chronic bronchitis and cough, in some cases accompanied by intensive expectoration, and ultimately to emphysema. The condition progresses insidiously. The progressive tendency for the vital capacity to decrease often precedes a stage of advanced pulmonary damage. In middle life the sufferer may be condemned to chronic invalidism. Radiographic appearances of patients in the late stage showed changes consistent with those of chronic bronchitis and emphysema except that the bronchial shadows were of a greater intensity.

In the mills it has not been found possible to prevent the cotton dust from escaping into the atmosphere. Improved air conditioning, in conjunction with improved dust extraction, is necessary. In the author's opinion, the best protection is offered by a careful selection of operators for the card room and regular examination of existing workers. Those types likely to be susceptible to the disease should be excluded. Protective respirators are advised for all operators.  
MARGARET H. WILTON

**The Care of the Aged.** Rowntree, B. S., *Industrial Welfare & Personnel Management*, 29: 46, 1947.

Many old people today are suffering acutely from remediable causes and the need to take steps to better their lot is urgent. This is particularly obvious when



it is remembered that the age structure of the population is changing and that in future years the proportion of pensionable age (65 for men and 60 for women) will increase rapidly and materially.

In this article the author, who presides over the Committee appointed in 1944 by the Nuffield Foundation Trustees, to consider the problem of ageing and the care of the aged, draws attention to those aspects of the question which he considers of special importance. He reviews progress in the matter of economic circumstances. Under the National Insurance Act of 1946, the former system of old age pensions is replaced by universal retirement pensions, which will mean that old people need no longer (save in exceptional circumstances) live below the poverty line.

A survey conducted by the Committee appointed under the Nuffield Foundation together with investigations by the author in 1936 yielded reliable information regarding the living conditions of the old people. A very large percentage of them are living independent lives in private houses, either as householders or otherwise. On the whole, conditions are neither better nor worse than those which obtained generally among the classes of people concerned but old people are apt to suffer more from bad housing conditions than younger people. From the information gathered it was seen that old people want small houses. They do not like to be segregated in colonies; their dwellings should be built in groups of 8 or 12 among other houses, near their old haunts and near to such amenities of life as shops, bus stops, a cinema and a place of worship.

The author emphasizes the suffering caused by loneliness and the need for the establishment of clubs for old people in every town, also the need for more nursing care and for home helps. He refers too, to the fact demonstrated during the war, that many old people can render valuable service in industry and he suggests that employers who have a fixed retiring age for their employees should consider whether in view of the present and prospective shortage of manpower, such a policy is in the national interest.

MARGARET H. WILTON

## OBITUARIES

**Dr. Byron Rayleigh Burwash**, aged 64, died recently at Saskatoon, Sask. He graduated from Toronto in 1911 and registered in Saskatchewan in 1912. He practised for some years at Hawarden, Sask., and for the past thirteen or fourteen years in Saskatoon, where he specialized in anaesthesia. Surviving besides his widow and his mother, are one son, and two daughters.

**Dr. James Anthony Cummins**, of Hamilton, died recently of a heart attack while vacationing in Muskoka, aged 44 years. Widely-known for his work in psychiatry and author of many articles published in both Canadian and American medical journals, Dr. Cummins joined the staff of the Ontario Hospital, Hamilton, in 1936. He left to set up private practice in Hamilton in 1944.

Born in Belleville, he graduated from Queen's University in 1930, and interned at the Ottawa General Hospital and Hotel Dieu, Kingston. He joined the staff of the Ontario Hospital at Whitby in 1931, later taking postgraduate work in Toronto. He attended St. Michael's College in Toronto, and Albert College, Belleville.

He is survived by his widow, two sons, a daughter, his mother, a brother and two sisters.

**Dr. Cameron W. Elmore** died at his home, Beamsville, Ont., on August 12. He was in his 64th year.

He is survived by his widow.

**Dr. Henry Ewart Gladstone Hinds** died suddenly at Sixteen Island Lake on August 3. He was in his 39th year.

A native of Westmount, Dr. Hinds received his early education in local schools, graduating from the

Westmount High School with the highest marks in the Province. He received a B.Sc. degree (*cum laude*) at McGill University and later went to McMaster University where he received the degree of Bachelor of Theology.

Following his graduation there he went to New College, Edinburgh, receiving a Ph.D. there. He then accepted a call from the King Street Baptist Church, Kitchener, Ont., where he served as minister for five years. In 1939 he was one of the leaders to the World Conference of Christian Youth which met in Amsterdam, Holland.

For reasons of health he was compelled to leave the ministry and, after returning to Montreal, studied medicine at McGill University, receiving the degrees of M.D., and C.M. In his final year he won the Lieutenant-Governor's Silver Medal in the field of public health.

After serving in the McGill Department of Pathology he became assistant psychiatrist of the Mental Hygiene Institute and while there gained a research fellowship in psychiatry from New York University. With this scholarship he went to Bellevue Hospital in New York, where he studied under Dr. Loretta Bender. Early this year he returned to Montreal and became associated with McGill University, the Montreal General Hospital and the Mental Hygiene Institute as psychiatrist. He was also active in boys' work and belonged to the National Council of the Y.M.C.A.

He is survived by his widow, a son and daughter, his parents, and a sister.

**Dr. John Jackson**, of Edmonton, passed away on August 25, 1947. He graduated from Queen's University in 1910, and registered in Alberta in 1912. He practised in the City of Edmonton until a few years ago, when he retired.

**Dr. Allan M. Lafferty**, a pioneer physician of Lethbridge, died August 4, following a long illness, at the age of eighty-six years. He graduated from McGill University in 1887 and came to Lethbridge, then in the Northwest Territories, in 1889, where he practised until a few years ago. He is survived by one son, Alan, of Los Angeles, California, and a daughter, Mrs. T. J. Love, of Lethbridge.

**Dr. Peter A. MacDonald**, aged 72, of Edmonton, passed away on August 17. Dr. MacDonald was a graduate of Western University. He came to Alberta in 1917 and shortly after arrival commenced practising in the coal branch district of Alberta, where he continued to practise until he was taken ill five years ago. During the past few years he has been doing locum tenens work.

**Dr. Ronald John MacDonald** died suddenly at his home in Antigonish on September 3. He was born at Fraser's Grant, Antigonish County in 1876. Following graduation from Tuft's Medical College in 1907 he practised in Aguathuna, Newfoundland, until 1938 when he returned to Antigonish, where he continued to practise until his retirement due to ill health about four years ago.

Dr. MacDonald was at one time a noted long distance runner, winning the Boston Marathon in 1898, and was a member of the American Olympic Team competing in Paris in 1900.

**Dr. Fred Holland Mackay** died on September 7 at the Private Patients' Pavilion of the Western Division of the Montreal General Hospital. He had been ill in the hospital since July 19.

A sportsman as well as an eminent scholar, Dr. Mackay led a varied and interesting life. Born in Prince Edward Island in 1884, he was educated at the Prince of Wales College at Charlottetown and later taught school.

For a time he worked in a C.P.R. construction camp in Western Canada where he met a young doctor—a meeting that was destined to determine his career.



He became friends with the doctor, whose name was King, and helped him with anaesthetics. King, who was later to become a Senator and leader of the Liberal Party in the Senate, inspired young Mackay to go to McGill and study medicine.

Following his graduation as a gold medallist from McGill University in 1912, Dr. Mackay became an intern at the Royal Victoria Hospital and was admitting officer there until the outbreak of the First World War. He joined the army and went overseas with the first Canadian contingent on the staff of No. 2 Canadian General Hospital.

In England Dr. Mackay volunteered to go to France with the Royal Army Medical Corps. He served with distinction at No. 2 Stationary Hospital (British) there, and later was recalled to his former unit, rejoining the Canadians at No. 2 General Hospital in Treport, France.

It was during that period that an event occurred which was instrumental in deciding the career in which he so distinguished himself. A great many "shell-shocked" soldiers were arriving at the base and Dr. Mackay was detailed to look after them. Thus he became interested in that type of case. On his return to England he had further experience in these cases while in charge of medicine at the Canadian Centre, Buxton.

When the war ended, Dr. C. F. Martin of Montreal, advised Dr. Mackay to take up neurology and so the latter spent a year at Queen's Square. On his return to Montreal, he became assistant neurologist at the Royal Victoria Hospital. He also did outstanding work in the care of war veterans who were mentally ill.

When Dr. Shirres resigned as neurologist of the Montreal General Hospital a few years later, Dr. Mackay was offered the position. He accepted the appointment and until the time of his illness in July of this year served in that capacity with great distinction.

Although a busy physician, Dr. Mackay still found time for other interests and was known for his knowledge of history and English literature. He also was interested in sports, particularly fishing, and was a member of the New Orleans Fish and Game Club, north of Quebec. He belonged also to the Royal Montreal Golf Club and the University Club.

He was president of the Montreal Medical Chirurgical Society and a member of the American College of Neurologists. He was also professor of Clinical Neurology at McGill University.

His first wife predeceased him in 1935 and he married Mrs. Mildred Russell Brodie, who survives him. He also leaves a son and daughter by his first marriage, Kenneth C. Mackay and Nancy H. Mackay.

\* \* \*  
AN APPRECIATION

Fred Mackay was one of those unusual men who fulfilled the promise of his university brilliance. He won the Holmes gold medal at McGill, which is awarded for the highest aggregate of marks throughout the medical course, and, in football language, from then on he was never headed. What used to impress me as his junior in college was the apparent ease with which he earned his honours. Some of the other men in his class who ran him close in honours, showed their concentration, but if Fred wasn't playing a joke, or telling stories with inscrutable expression, then he would be leading a song in harmony with "Nibs" McLeod and some of his other bosom friends. And this was no pose to set off his scholastic achievements. It was a natural love of fun which was developed in him to its highest degree. Perhaps it was this love of simplicity which played so large a part in his success as a neurologist. At the time that he took up neurology it had not then become as sharply differentiated as it now is from psychology and psychiatry, and if there ever was anyone who could combine these three aspects it was he. He had a complementary shrewdness and knowledge of men which made him the ideal consultant in this field. And he never

allowed his work to either sour or depress him. He saw enough of the ugliness of disease, as all psychologists do, to excuse dejection, but his mind was always sunny.

"With summer lightnings of a soul  
So full of summer warmth, so glad,  
So healthy, sound, and clear and whole  
His memory scarce can make me sad."

He had one of the largest and most burdensome clinics in the Outdoor Department of the Montreal General Hospital, but not until his own health broke down did he give up the work. Never a week would go by but one could see him waiting for clinic time in the doctors' sitting room, immersed in the cross-word puzzle of the day.

Men with such powers of mind as his often unconsciously create barriers between themselves and others, ranging from stiffness to aversion. But he was readily approachable, and never allowed his quick wit to offend. Not but what he was a good talker and loved the rough and tumble of an argument. He knew the best literature and was hard to equal in quotation from the Bible and poetry.

How rare are such men; who have such gifts of mind and personality; spending them so finely to the very end.  
H.E.M.

Dr. William Edward Macklin died suddenly at Guelph General Hospital on August 8. He was a medical missionary, formerly of Nanking, China. Surviving are four sons and two daughters.

Brig. C. H. Playfair, aged 47, died on August 13 in his home on the Mountain Sanatorium grounds at Hamilton, Ont.

Born in Playfair, Ont., Cecil Homer Playfair studied in high school at Arnprior, Ont., and at Queen's University in Kingston. Graduating in medicine in 1924 he took postgraduate studies in New York, starting his practice in 1926.

Brig. Playfair, from lessons of Allied defeats in France and Norway and the subsequent Allied seizure of Spitzbergen, when he accompanied the invading Canadian forces, was mainly instrumental for sweeping reorganization of the Canadian forces' medical services in the field during the Sicilian and Italian campaigns.

He received the Order of the British Empire early in the war. In 1945 at Buckingham Palace the King conferred the Commander of the Order of the British Empire upon him.

He is survived by his widow, one son and one daughter.

Dr. Wilfred Gordon Joseph Poirier died at Cheticamp on August 14. He was born in Halifax, November 2, 1896. After graduation from Dalhousie University in 1924, he practised for brief periods at Mulgrave and Inverness before settling in New Waterford where he practiced seven years. About fifteen years ago he moved to Cheticamp, where he built up a large and extensive practice. He was a veteran of World War I.

Dr. H. William Riley, aged 31, of Winnipeg, died on August 26. He graduated in medicine from the University of Manitoba in 1939 and spent one year in the Winnipeg General Hospital as resident in medicine. Enlisting with the R.C.A.F. in 1940 he had a distinguished record, serving in the Shetland Islands, Ceylon, and Burma. He rose to the rank of Squadron Leader; in 1943 was a senior medical officer with the R.A.F. wing in the South East Asia air command. He spent a few months at the Rheumatic Fever Hospital in Calgary in 1944 and since then has been connected with Deer Lodge Hospital, Winnipeg, and with the Winnipeg Clinic. He was a member of St. Aidan's Church and the Zeta Psi fraternity. He is survived by his widow, a son and daughter.

**Dr. Estella Olive Smith** died on July 3. Surviving is one sister.

**Dr. William C. White**, of Washington, D.C., died on August 10, after an illness of several weeks. He was in his 73rd year.

Born in Woodstock, Dr. White graduated in medicine from the University of Toronto and later did postgraduate work in Europe.

Outstanding in medical circles, he served as a professor of neuro-anatomy and clinical psychiatry at Indiana University and as professor of medicine at the University of Pittsburgh. In 1921 Dr. White headed the committee for the construction of tuberculosis hospitals in the United States and later served for 26 years as chairman of the National Tuberculosis Association.

Surviving are two daughters, four sisters and one brother.

**Dr. E. J. F. Williams**, aged 69, died recently at Brockville, Ont., where he had practised medicine for 41 years.

**Dr. Frank S. Young**, physician and surgeon at Seeley's Bay, Ont., for 40 years, died recently after a brief illness. He had been active until the time of his death.

Born at Forfar, he took an active part in fraternal societies. He was a past district deputy grand master of Frontenac District Masonic Lodges, first worthy patron of the Eastern Star, which was organized in Seeley's Bay last year, and was a past grand of Seeley's Bay IOOF Lodge. He graduated from the Athens High School and later the faculty of medicine at Queen's University.

Dr. Young was medical officer for the rear of Leeds and Lansdowne Township, coroner for the County of Leeds and for some years was a member of the Seeley's Bay School Board.

Besides his widow he is survived by two sons, two daughters, and three grandchildren.

## NEWS ITEMS

### Alberta

Medical care of recipients of pensions from the Department of Public Welfare has been provided now for the past two months. The number of individuals taking advantage of the service is very high. If it continues so, it is very doubtful if the profession will be paid much more than 50% of the schedule of fees.

Plans for the establishment of a Province-wide voluntary pre-paid medical scheme have been delayed owing to Provincial regulations regarding incorporation. It will be necessary to apply for incorporation by private bill at the next session of the Alberta Legislature.

District Medical Societies have started their fall meetings with a meeting at Castor on August 29, and at Olds on September 3. It is expected that the other district medical societies will be active by mid-October.

**Dr. A. W. Park** of Calgary has been made a life member of the College of Physicians and Surgeons and of the Canadian Medical Association, Alberta Division. Dr. Park graduated from McGill University in 1904, and came to Alberta shortly after graduation. For many years, Dr. Park was administrative medical officer for the Department of Pensions and National Health in Calgary. He retired from this position in 1946.

G. E. LEARMONTH

### British Columbia

The Annual Meeting of the British Columbia Medical Association for 1947 was held at the Hotel Vancouver, in Vancouver, from September 17 to 19 inclusive. There was an excellent list of speakers including the following: Dr. F. G. McGuinness, Winnipeg, Professor of Obstetrics, University of Manitoba; Dr. F. A. L. Mathewson, Winnipeg, Lecturer in Medicine, University of Manitoba; Dr. K. R. Trueman, Winnipeg, Demonstrator in Surgery, University of Manitoba; Dr. A. W. Blair, Regina, Director of Cancer Services, Province of Saskatchewan; Dr. G. Lyman Duff, Montreal, Professor of Pathology, McGill University; Dr. E. J. Washington, Winnipeg, former Head, Department Otolaryngology, University of Manitoba.

An extensive program of entertainment for the wives and daughters of those attending this convention was arranged under the chairmanship of Mrs. L. H. Leeson, assisted by a large committee. Fuller details will be given later.

**Dr. and Mrs. J. H. Rivers**, formerly of Lethbridge, where Dr. Rivers formerly practised, celebrated their golden wedding this year, and received the congratulations of their many friends on the occasion.

**Dr. B. F. Keillor**, Canadian Pensions Medical Examiner for over 29 years, has retired at the age of 66. He has been head of the Canadian Pensions Committee since 1931, and had his headquarters at Shaughnessy Hospital in Vancouver. He was presented with a travelling bag at a farewell party given in his honour at that Hospital. He was a graduate of Toronto University Medical School, and served overseas from 1915 to 1918 in the R.A.M.C., and the R.C.A.M.C.

**Dr. G. L. Watson**, recently in practice in Vancouver, has assumed the duties of Medical Director of the M.S.A. of B.C. Dr. Watson succeeds the late Dr. C. H. McEwen, and is eminently suited for the position, as he worked with Dr. McEwen for quite a time, and is well-known to the medical men of British Columbia.

Recent marriages, of interest to British Columbia, are as follows: Dr. William Leonard Grant, Vancouver, to Miss Kathleen Allen, of Victoria. Dr. John L. McMillan, of Vancouver, now at the Vancouver General Hospital, to Miss Ruth Walker, of Kingston, Ont. (married in Quebec). Dr. J. E. Harrison, of Vancouver, to Alice R. Scharfe. Dr. John N. Neilson, of Vernon, B.C., to Miss Elizabeth Sovereign. J. H. MACDERMOT

### Manitoba

Manitoba Medical Service has dissociated itself from the Manitoba Hospital Service Association which formerly acted as agent for securing new members and collecting fees. Manitoba Medical Service has moved to bright and commodious quarters in a new building on Portage Avenue East.

Changes are being made in Class room A and the old anatomy theatre of the Medical College to provide additional space for the new freshman class in medicine which will start in September. The new class will number 90, an increase of about 50% over previous freshman classes.

The corner stone of the Shriners' new hospital on Wellington Crescent, Winnipeg, was laid August 16 with appropriate ceremonies.

Because of the large number of poliomyelitis cases it may be necessary to open another ward in King George Hospital, Winnipeg. Up to August 25 about 350 cases had been reported. A total of 9 cases of encephalitis had been reported, all except one in rural Manitoba.

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Fortunately the poliomyelitis has been for the most part of mild character.

An archaeological survey is being conducted at Lockport near St. Andrews rapids on the Red River. This was a favorite camping ground of Indians. The survey has uncovered two occupations where the Indians were almost wholly fish-eaters.

Dr. R. E. Beamish of Winnipeg has been awarded a Lord Nuffield travelling fellowship and has left for London, accompanied by his wife. He will commence postgraduate study at the London Postgraduate hospital.

Dr. F. G. McGuinness, president of the Canadian Medical Association and head of the department of Obstetrics and Gynaecology of the University of Manitoba, has been elected a Fellow of the Royal College of Obstetricians and Gynaecologists, London.

In memory of the late Dr. B. J. Brandson of Winnipeg a bronze plaque was unveiled in the Gimli Old Folks Home on August 23. Inscribed in Icelandic, the plaque reads: "Dr. B. J. Brandson, born June 1, 1874, died June 20, 1944. He had the welfare of the aged at heart. He was a true and staunch supporter of every just cause." Dr. Brandson was president of the Board of Directors of the Gimli Old Folks Home in 1915 and worked for the home until his death.

Dr. H. M. Edmison, who for several years has been associated with Dr. Digby Wheeler, is leaving Winnipeg shortly to take up his residence in Victoria, B.C. where he has accepted a position in the department of radiology of the Royal Victoria hospital. ROSS MITCHELL

### New Brunswick

Dr. J. Clarence Webster, of Shediac, was paid a well deserved tribute by the Board of the New Brunswick Museum on July 30 when he was presented with his own portrait, painted by Charles MacGregor, A.R.C.A. and O.S.A. Dr. Webster, one of New Brunswick's most famous medical men, having left many enduring additions to medical knowledge during a long active medical career, turned his interest, industry and special gifts to the study of the history of the Maritime Provinces and especially his native Province of New Brunswick. With utter disregard to passing years his enthusiasm has continued and his accomplishments in seeking out historical sites, documents and portraits and placing these finds in suitable sanctuaries throughout the Maritimes has perpetuated our history and made available for coming generations the legend and glamour with which Maritime history was and is filled.

Dr. Webster was eulogized by experts at the function at the Museum and all of us are proud to join in his praises for his work in historical research and at the same time recall his many accomplishments as a physician, which are sometimes lost sight of as his fame as an historian becomes greater. Dr. Webster has always retained a first hand interest and up to date viewpoint on advances in medicine, and particularly his interest has been keen in the physicians who have made these advances possible. Dr. Webster's interest in people as individuals is perhaps one of his finest characteristics.

The newspaper announcement that the Federal Government was contemplating the inclusion of physicians from Europe in the group of displaced persons eligible for entry to Canada has caused some thought on the part of physicians charged with the maintenance of the high standards for doctors practising in this country. It is apparent that the supply of doctors in the towns and cities of Canada is sufficient for in fact many of our cities seem to have already attracted an excess of medical practitioners. The

rural areas of Canada would then be the place where these displaced physicians might perhaps be needed, but two things argue against their success in this field. The background and training of central European physicians hardly fit them for the rugged conditions in our sparsely settled areas and the conservatism of the Canadian rural population is so well known that their reception of a physician of a strange race and tongue might not be too warm.

Hon. Dr. F. A. McGrand has announced that the Government of New Brunswick has added to its already excellent health service a Province wide cancer diagnostic service. These diagnostic centres will be spotted in strategic hospitals already existing and will be in charge of specially chosen doctors. The administration and correlation of the new service will be carried out by Dr. D. F. W. Porter the director of hospital services. The professional and clinical aspects of the new service will be in the hands of a three man advisory committee, Dr. J. R. Nugent, Chairman and Surgical Consultant; Dr. R. A. H. MacKeen, Pathological Consultant and Dr. A. S. Kirkland, Radiological Consultant. The advisory committee have operated the Tumour Clinic in Saint John for several years.

All patients are to be referred to the clinics by their own physician to whom reports will be submitted. There is no means test involved, all residents of the Province will have free access to this new service. A. S. KIRKLAND

### Nova Scotia

Dr. Joseph A. MacDougall has been appointed anaesthetist on the staff of St. Martha's Hospital, Antigonish.

Among the homes seriously endangered by the recent forest fires in Antigonish County was that of Dr. William Chisholm who spends his summers at Cape George. A barn nearby was burned and the flames came within a few yards of the house.

Dr. Adelaide Fleming and Dr. Jean MacDonald have opened an associated practice in Halifax. Dr. Fleming will give special attention to paediatrics.

Dr. Eric Fergus John Dunlop, a graduate of Edinburgh University in 1929 has opened a practice in Bridgewater, confining his work to diseases of the Eye, Ear, Nose and Throat.

Dr. Robert Begg, Assistant Professor of Biochemistry at Dalhousie University has been given a grant by the National Research Council to continue his work in Cancer Research.

Dr. John Cameron of Bournemouth, England, Professor of Anatomy at Dalhousie University for sixteen years, from 1914 to 1930, is spending three weeks visiting former friends and acquaintances in Nova Scotia. H. L. SCAMMELL

### Ontario

Dr. Robert Bews Kerr has been appointed Assistant Professor of Medicine and Head of the Department of Therapeutics in the University of Toronto. During the war he attained the rank of Lieut.-Col. R.C.A.M.C. and was honoured with the award of the Order of the British Empire for distinguished service. He succeeds Professor Ray Farquharson who held this post before being called to succeed Professor Duncan Graham.

Dr. Ian MacDonald succeeds Dr. Farquharson as Director of Medical Services for the Department of Veterans' Affairs in the Toronto district.



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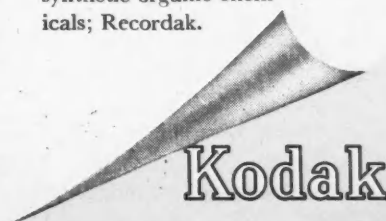
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Dr. M. J. McHugh is retiring from the superintendency of the Toronto Hospital in Weston after twenty-nine years' service. He is to be succeeded by Dr. C. A. Wicks who, since 1945, has been Director of the Gage Institute in Toronto.

Dr. W. E. Gallie and Dr. E. Stanley Ryerson, formerly Dean and Assistant Dean of the Faculty of Medicine, University of Toronto, have been awarded the King Haakon VII medal by the King of Norway. The honour is in recognition of services rendered to Norwegian medical students who studied in the University of Toronto when forcibly expatriated during the war.

M. H. V. CAMERON

Cancer research should make some progress in Canada in the coming year. The national Cancer Institute of Canada has awarded more than \$100,000 in grants to twenty faculty members of Canadian universities for cancer research. More than fifty workers will devote their time and energies to this work. Those receiving the grants are: Professor John Gray Aldous, Professor Robert William Begg, Professor F. Roland Hayes, and Professor D. Pelluet of Dalhousie University; Professor N. J. Berrill, Professor C. P. Leblond, and Dr. Samuel Albert of McGill University; Professor Kenneth C. Fisher, Professor W. R. Franks, Professor Arthur Ham, Dr. Jeanne Manery, Dr. Raymond C. Parker, Professor A. M. Wynne, Professor C. E. Van Rooyen, and D. W. A. Roberts, B.A., of the University of Toronto; Professor D. Nicholson, and Professor H. V. Rice, of the University of Manitoba; Professors J. J. Ower and J. W. McGregor, of the University of Alberta; John D. Hamilton, M.A., of the University of Western Ontario; Professor L. C. Simard of the University of Montreal.

In addition to these grants, the Ontario Cancer Treatment and Research Foundation has awarded over \$75,000 for cancer research in Ontario. The grants have been given to Professor Arthur W. Ham, Department of Anatomy; Professor E. F. Burton, Department of Physics; Dr. Raymond C. Parker, Connaught Laboratories; Professor Bruno Mendel, and Professor W. R. Franks of Banting and Best Department of Medical Research; Dr. P. J. Moloney, Connaught Laboratories; Professor K. C. Fisher, Department of Physiology; Professor H. B. VanWyck, Department of Obstetrics and Gynaecology; Professor E. W. McHenry, Department of Hygiene, all of the University of Toronto. Dr. Helen Bell Milburn, Women's College Hospital, Toronto; Professor R. G. Sinclair, Department of Biochemistry; and Professor Edwin M. Robertson, Department of Obstetrics and Gynaecology, of Queen's University; Professor J. H. Fisher, Department of Pathology; and Dr. Ivan H. Smith, Victoria Hospital, London; and Dr. M. L. Barr, Department of Anatomy, all of the University of Western Ontario; Dr. A. R. Armstrong, Mountain Sanatorium, Hamilton.

The health committee of the Canadian Life Insurance Officers' Association has made a grant to the Hospital for Sick Children, Toronto, for the study of poliomyelitis. The work is to be under the supervision of Dr. L. N. Silverthorne.

The Medical Alumni of the University of Toronto is holding a two-day refresher course at the Toronto General Hospital and the Banting Institute, October 22 and 23. On Wednesday evening, October 22, a dinner will be held in the Royal York Hotel.

Dr. James A. Dauphinee has been appointed Professor of Pathological Chemistry at the University of Toronto. A graduate of the University of British Columbia he obtained his M.D. degree with honours from the University of Toronto, Faculty of Medicine, and his M.A. and his Ph.D. in biochemistry from the University of Toronto. He joined the Canadian Army early in 1940, went overseas and became O.C. Medicine of No. 8 General Hospital, serving in England and

Northwest Europe. He was decorated with the Order of the British Empire.

The Medical Alumnae Association of the University of Toronto elected the following officers at its annual meeting:

Honorary President, Dr. Catherine Woodhouse; Past President, Dr. Jean Davey; President, Dr. Mary Jackson; 1st Vice-president, Dr. Dorothy Daley; 2nd Vice-president, Dr. Evelyn Bateman; 3rd Vice-president, Dr. Jean Leeson; 4th Vice-president, Dr. Frances H. Stewart; Out-of-town Vice-president, Dr. Margaret Patterson Campbell, London; Treasurer, Dr. Doris Monypenny; Secretary, Dr. Margaret Quentin.

In August and September, Dr. H. S. Dunham, Executive Secretary of the Ontario Medical Association, accompanied by his wife who is a graduate of the Hamilton General Hospital, made an extensive motor tour of the northern part of Ontario. They visited Sioux Lookout, Dryden, Red Lake, Kenora, Rainy River, Emo, Fort Frances, Port William, Port Arthur, Red Rock, Nipigon, Schreiber, Beardmore, Geraldton, Hearst, Kapuskasing, Moonbeam, Smooth Rock Falls, Cochrane, Timmins, Iroquois Falls, Kirkland Lake, Englehart, New Liskeard, Haileybury, Cobalt, Timagami, Sudbury, North Bay, Gravenhurst, and Barrie.

They attended the 3-day meeting of District Number Ten, comprising Kenora, Rainy River, Patricia, and Thunder Bay, held in conjunction with the Lakehead Summer School at Fort William and Port Arthur. Speakers at this School were: Dr. W. F. Connell, Kingston, Dr. C. W. Harris, Toronto, Dr. E. H. Botterell, Toronto, and Dr. M. C. Dinberg, Toronto. They attended the annual meeting of District Number Nine, comprising Algoma, Temiskaming, Sudbury, Nipissing, Cochrane, Parry Sound, Muskoka and Manitoulin, at the Muskoka Beach Inn, Gravenhurst. The speakers at this meeting were: Dr. R. J. Galloway, Dr. J. R. Card, Dr. J. F. McCreary, Dr. Jacob Markowitz all of Toronto, Dr. C. B. Ross, Gravenhurst.

They also visited the annual meeting of District Number Five at Barrie. Dr. J. E. Carson of Brantford, President-elect of the Ontario Medical Association, attended the annual meetings of the Districts.

The portrait of Dr. R. I. Harris by Cleeve Horne at the Canadian National Exhibition attracted much comment. He stands gowned, capped, and not completely unmasked with a pencil and pad in one hand apparently about to make a sketch of the operation just completed. The picture, done with a light palette, is pleasing rather than strong but is a change from the conventional college-gown likeness.

Dr. W. E. Gallie, recently retired head of the Department of Surgery of the University of Toronto, has been awarded the honorary medal of the Royal College of Surgeons of England. An announcement following a recent meeting of the organization states that Dr. Gallie is one of 20 medical men to receive the award since its institution in 1802. Others have been Sir James Paget, Lord Lister and Sir George Makin. LILLIAN A. CHASE

### Quebec

A Diploma in Tropical Medicine is given by the Faculty of Medicine, McGill University, Montreal. During the war years a short course was available to members of the armed forces. As a result of this experience, the curriculum has been revised, and additional facilities provided to give medical graduates a broader training for tropical practice. The course is being conducted by the Department of Health and Social Medicine with the collaboration of other departments in the Faculty of Medicine and the assistance of members of other Faculties in the University.



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A modification in the concentration of pertussis vaccine has recently been made by the Connaught Medical Research Laboratories, so that the vaccine formerly containing 15,000 million killed organisms (*H. pertussis* from strains in Phase I) per cc. now contains approximately 22,500 million killed organisms per cc., permitting the administration of three doses of 1 cc. at monthly intervals, and a reinforcing dose of 1 cc. after an interval of at least three months.

## DIPHTHERIA TOXOID AND PERTUSSIS VACCINE (Combined)

Diphtheria toxoid has been combined with the new concentration of whooping cough vaccine. The new combined product is also administered in three doses of 1 cc., with a reinforcing dose of 1 cc.

## DIPHTHERIA TOXOID, PERTUSSIS VACCINE AND TETANUS TOXOID (Combined)

For protection against tetanus as well, a triple antigen has been introduced by the Laboratories. This product contains diphtheria and tetanus toxoids combined with the new concentration of whooping cough vaccine and is administered in three doses of 1 cc., followed by a reinforcing dose of 1 cc.

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*The reinforcing dose is included in each package.*

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The Tenth Annual Louis Gross Memorial Lecture will be delivered at the Jewish General Hospital, Montreal, under the auspices of the Montreal Clinical Society, on Wednesday, October 29, 1947, at 8.30 p.m., by Dr. I. Arthur Mirsky, Director of the May Institute for Medical Research, and Associate Professor of Experimental Medicine in Psychiatry, University of Cincinnati. The subject will be "Biology of Metabolic Disease in Man".

Les 10 et 11 septembre le Collège des médecins et chirurgiens de la province de Québec a fêté le centenaire de sa fondation. Le numéro d'août de l'*Union Médicale* a été consacré aux commentaires de cet événement; on pourra y lire d'intéressants articles se rapportant directement ou indirectement aux activités du Collège.

Le Dr Jean Grégoire, sous-ministre de la Santé de la province de Québec a représenté l'Université Laval au congrès de l'enseignement de l'hygiène scolaire et universitaire à Paris. Il a également participé au congrès des services sociaux catholiques qui s'est tenu à la fin de juillet.

JEAN SAUCIER

### Saskatchewan

While cases of poliomyelitis are still being reported in Regina, the control of the disease appears to be satisfactorily organized. A diagnostic clinic to which all cases are referred for a detailed examination has been established. Committees have been appointed, diagnostic criteria laid down, and patients found suffering are at once admitted to the isolation wing of the Regina General Hospital. All other suspects are returned home with careful instructions and asked to return to the clinic immediately on development of symptoms.

The committee on treatment has drawn up a set of standard procedures and while the attending physician continues to care for his patient, the method of treatment has been uniform in similar stages in development of the disease.

Committees have been named by the Medical Staff of both Hospitals in Regina to prepare a series of talks, lectures and demonstrations to the interns during the coming year. It was felt that these presentations should be on subjects not usually covered by the University course. "Office Practice," "Doctor and Patient Relationship," and "Rural Practice," are only a few of the headings suggested.

Dr. Alan Duncan, F.R.C.S. (Edinburgh), formerly of Dawson City, has moved to Regina and is at present associated with Drs. Ritchie, MacRae, McLean and MacMillan.

Dr. Roger M. Hall, (D.M.R. London) formerly radiologist at the Col. Belcher Hospital, Calgary, has arrived in Regina to take charge of the x-ray department of the Medical Arts Clinic.

First mental health clinic in Saskatchewan was opened recently in Weyburn and is expected to be the forerunner of others elsewhere in the Province. The Weyburn clinic is a joint project of the city school board, Weyburn larger school unit and the departments of education and health.

Dr. Duncan Graham, Toronto, recently appointed adviser in medical education to D.V.A., accompanied by Dr. Wallace Wilson, Western Regional Medical Officer for D.V.A., spent the day on July 15 in Regina. This was part of an organization tour covering all the centres.

At a recent meeting of the Saskatoon and District Medical Society, Dr. G. E. Dragan was elected President and Dr. C. B. Orchard elected Secretary-Treasurer.

B. BRACHMAN

### General

The Second Mexican Congress of Medicine is to take place in the General Hospital of Mexico City from November 9 to 15.

The following aspects of Tropical Medicine are to be discussed: malaria, Chagas' disease, leishmaniasis, uncinariasis, onchocerca, amœbiasis, leprosy and pinta.

Many distinguished Mexican and foreign investigators have agreed to present their work in this scientific reunion.

Dr. G. D. W. Cameron, Ottawa, deputy minister of national health, will be the Canadian delegate to the fourth meeting of the interim commission of the World Health Organization. The meeting was held in Geneva from September 1 to 13. Alternate delegate will be Dr. T. C. Routley, Toronto, general secretary of the Canadian Medical Association, and the advisers will be Dr. Léon Gérin-Lajoie, of Montreal; Dr. M. R. Bow, Edmonton, deputy minister of health for Alberta; and John Halstead, Department of External Affairs, Ottawa. Dr. Cameron will also serve as an adviser to the Canadian delegate to a meeting of F.A.O. which opened in Geneva on August 25. The F.A.O. delegation from Canada is headed by Rt. Hon. J. G. Gardiner, Minister of Agriculture. Following the Geneva meetings Dr. Cameron will attend as an observer the first full conference of the World Medical Association in Paris. Dr. Routley is chairman of the organizing committee of the W.M.A.

**Van Meter Prize Award.** The American Association for the Study of Goitre again offers the Van Meter Prize Award of three hundred dollars and two honourable mentions for the best essays submitted concerning original work on problems related to the thyroid gland.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia, not later than February 1, 1948.

Scientific studies of the poliomyelitis (infantile paralysis) virus are being undertaken by the Department of National Health and Welfare. The studies will be carried out in the Vancouver area under the direction of Dr. D. V. Hutton, paediatric specialist of the child and maternal health division of the Federal department, in collaboration with Dr. Stuart Murray, medical health officer for the metropolitan area of Vancouver, and assisted by the pathologists and staff of the Vancouver General and St. Paul's Hospitals.

With the co-operation of paediatricians and general practitioners, it is hoped to obtain the virus from each patient at three stages of the disease: the active stage; again, following the disappearance of fever; and finally in later convalescence. The clinical and pathological material obtained will be refrigerated and sent by air under refrigeration to Ottawa where special experimental facilities are being provided by the Laboratory of Hygiene. The Ottawa experiments will be conducted by the Laboratory of Hygiene's virologist, Dr. J. W. Fisher, and are expected to take at least six months to complete.

Cultures will also be obtained from persons in the same area who have not contracted polio. These will in as many instances as possible be from families of polio victims and will be used for comparison with the cultures taken from those who have the disease.

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Two physicians to His Majesty the King—Dr. John A. Ryle and Lord Horder—have accepted appointments to the Board of Honorary Advisory Directors of the Health League of Canada, it has been announced by H. H. Bishop, League president. Both physicians recently visited Canada. Dr. Ryle has been Physician Extraordinary to the King since 1936. He also is director of the Institute of Social Medicine, Oxford University, and consulting physician to Guy's Hospital. Lord Horder is Physician in Ordinary to the King, and is consulting physician at St. Bartholomew's Hospital.

## BOOK REVIEWS

**Music in Hospitals.** W. van de Wall, Head, Adult Education Section, Education Branch Internal Affairs and Communications Division Office of Military Government for Germany, U.S. 86 pp. \$1.00. Russell Sage Foundation, New York, 1946.

For twenty-five years, ever since its inception into hospitals, notable progress has been made in the systematic application of music as a means of occupational therapy and of relaxation. During the war years musicians were inspired to make an important contribution with their art; the end of the war has not reduced the demand for this contribution. Music in Hospitals deals particularly with those aspects that need clarification and development. The solution of basic problems, common to all hospital situations in the presentation of musical programs, is presented, not as final conclusions, but as sound advice based on practical experience and offered for the purpose of information and stimulation.

The musician is acquainted with the processes of involuntary physical and mental responses in order to impress upon him his responsibility in planning to render service to the hospital through a musical program. Emphasis is placed on the joint musical participation of patients, hospital personnel and outside talent as symbolic of the function of the hospital as a humanitarian agency that successfully furthers the health and happiness of the community. Some good advice is given about the early establishment of mutual understanding between the hospital administrator and the musician; practical integration of a music-activities program, and orientation of music as to treatment and therapy.

**Group Psychotherapy.** J. W. Klapman, Faculty, Northwestern University Medical School, Chicago. 344 pp. \$4.00. Grune & Stratton, New York, 1946.

Psychotherapy in general is still much of an art and the therapist's own intuition and personality are unfortunately of great significance in the results. This is particularly true of group psychotherapy. As Dr. Klapman points out in the preface of his book, "its concepts, theories and practices are still in the initial and fluid stage and there has yet been insufficient time and opportunity to precise formulations".

However the various reports published—some of them very enthusiastically—showing the usefulness of group psychotherapy and the pressure of numbers, has made a book like this necessary. In it, as its author states cautiously, one can find a "summation of current usages and, from a practical point of view, for purposes of guidance, although still largely tentative, principles for those who contemplate the use of this psychotherapy".

The author divides his book in three parts: I. Historical and Anthropological Considerations; II. Dynamics and III. Methods of Administration. In the I. and II. parts which in the reviewer's opinion are excellent, the author tries to establish the scientific basis for this procedure as well as the interpretation of its functioning. In the third part the author describes all the methods used by the different psychiatrists, including the psycho-

drama, though no evaluation of the various techniques described is clearly presented. The most detailed description given is that of the technique dealing with severe neurotic or psychotic indoor patients. Some attention is also given to the treatment of patients of the Outdoor Clinic and in a more lengthy way the treatment of dealing with problem children and their mothers is described, as well as the private psychiatric practice.

To write a book on group psychotherapy at the present stage is a really difficult task, but nevertheless it was absolutely necessary to have a certain guide in the present circumstances, particularly because of the great interest awakened by this procedure. In the reviewer's opinion, Dr. Klapman has done the best that could be expected and he has rendered a good service to the practice of psychotherapy. If one reads the book with the same cautiousness with which it was written, it will be found very useful.

**Radical Surgery in Advanced Abdominal Surgery.** A. Brunshwig, Professor of Surgery, University of Chicago. 324 pp., illust. \$7.50. The University of Chicago Press, Chicago, 1947.

This report of 200 consecutive cases of advanced and complicated abdominal cancer is based on the author's definition of the term "operable"; according to this concept an operable neoplasm is one which can be removed regardless of where or how much spread has developed.

Accordingly, the operations described include gastrectomy-spleno-pancreato-colectomy, total gastrectomy, total pancreatectomy, splenectomy, as well as total gastrectomy and partial hepatectomy. These massive resections are made possible by the recent developments in anaesthesia, shock research, the knowledge of fluid balance, and a greater appreciation of the nutrition of surgical patients. The advent of chemotherapy with sulfonamides and penicillin have contributed to the reduction in risk attendant on major surgical procedures. The mortality rate for the 100 cases was unavoidably high—34%; 14% are alive two to ten years after operation. This type of surgery is obviously limited to highly qualified men.

**Surgical Treatment of the Nervous System.** F. W. Bancroft, Associate Clinical Professor of Surgery, Columbia University; and C. Pilcher, Associate Professor of Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee. 534 pp., illust. \$20.00. J. B. Lippincott Co., Philadelphia, Pa., 1947.

The chapters listed in this volume cover the cranium, tumours, epilepsy, nerve disorders, spinal cord, autonomic nervous system, and peripheral nerves. As in the work on "The Soft Tissues", each topic is presented by an authority in that specialized section. An introductory chapter on neurosurgical technique is concise yet complete. The illustrations are adequate and well reproduced, and a comprehensive bibliography is included in each section. A special chapter is devoted to the use of anti-biotics in neurosurgery. This book is of particular value to postgraduate students in the specialty of neurosurgery.

**Surgical Treatment of the Soft Tissues.** F. W. Bancroft, Associate Clinical Professor of Surgery, Columbia University; and G. H. Humphreys, Valentine Mott Professor of Surgery, Columbia University. 520 pp., illust. \$18.00. J. B. Lippincott Co., Philadelphia, Pa., 1947.

This volume includes chapters on the surgical treatment of hernia, lesions of skin and face, plastic surgery, burns and freezing, infections, neoplasms, vessels and lymphatics, each written by an author outstanding in his particular specialty. The section on plastic surgery is a brief but excellent survey of this highly specialized field. The treatment of burns incorporates many of the experiences and methods developed during World War II. Photographs, diagrams and illustrations are numerous and add considerably to the value of this book as a manual for students. Each chapter is covered by an adequate bibliography.